

**Faculty of Science and Engineering
Department of Chemistry**

**Synthesis of a Benzene-Annulated Analogue of Resolvin E1 and other
Lipid Mediators**

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Doctor of Philosophy
of
Curtin University**

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Declaration

To the best of my knowledge and belief, this thesis contains no material previously published by any other person except where due acknowledgement has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

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Presentations, Awards and Publications

Oral Presentation:

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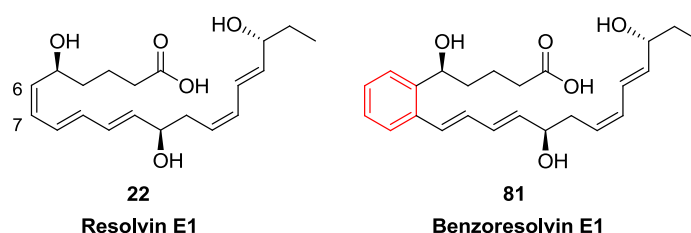
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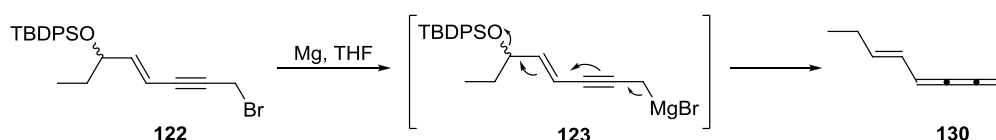
Most importantly I would like to thank my family for their support. To my Mum, your encouragement and unconditional love has propelled me to reach this point. In you I have found my biggest fan. To my Dad, sister and Mike, I am thankful for your constant words of encouragement. To my partner Vanessa, you have always been by my side. Words cannot describe how much I appreciate your love and support. Thank you for everything. Finally, to my Blue Nonna and Green Nonno, you were there for me when I was a baby, a young boy, a teenager and in my mid twenties. I am so sad that you will not see me graduate. I love you very much and dedicate this dissertation to you.

Abstract

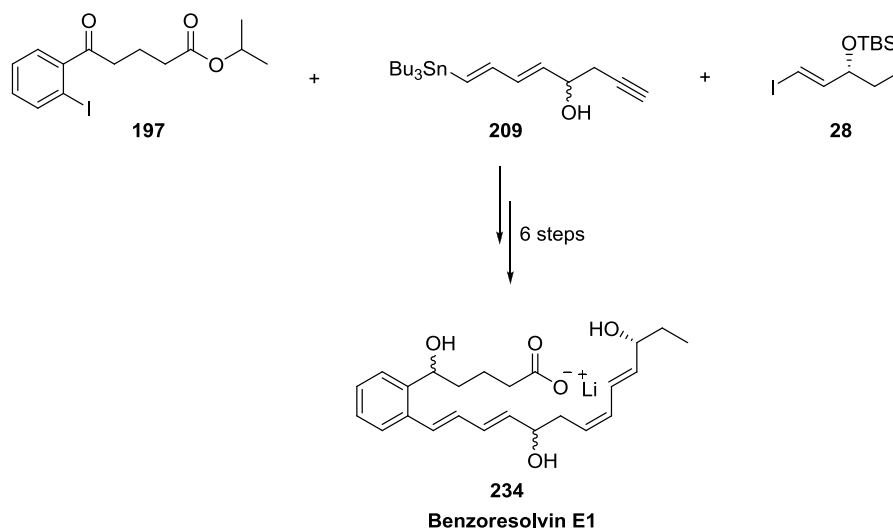
Resolvin E1 is a potent anti-inflammatory lipid mediator. At nanomolar levels, it is able to attenuate inflammatory responses such as leukocyte infiltration and pain. It is also chemically unstable and readily isomerises at the C₆–C₇ position. This gives the 6*E*-isomer which is no longer anti-inflammatory in action. The research described in this thesis outlines the synthesis of a benzene annulated analogue of resolvin E1, named benzoeresolvin E1. The inclusion of the benzene ring would improve the chemical stability of resolvin E1 by inhibiting the isomerisation pathway.



The first approach details the synthesis of the bromide **122** (Chapter 2). This compound was prepared in 4% yield in 8 steps. It could be converted into the Grignard **123** to give the C₁₃–C₂₀ portion of benzoeresolvin E1. Unfortunately, treatment of compound **122** with magnesium turnings led to degradation. It was postulated that upon formation, the Grignard reagent **123** eliminates TBDPSOMgBr to give the highly reactive cumulene **130**.

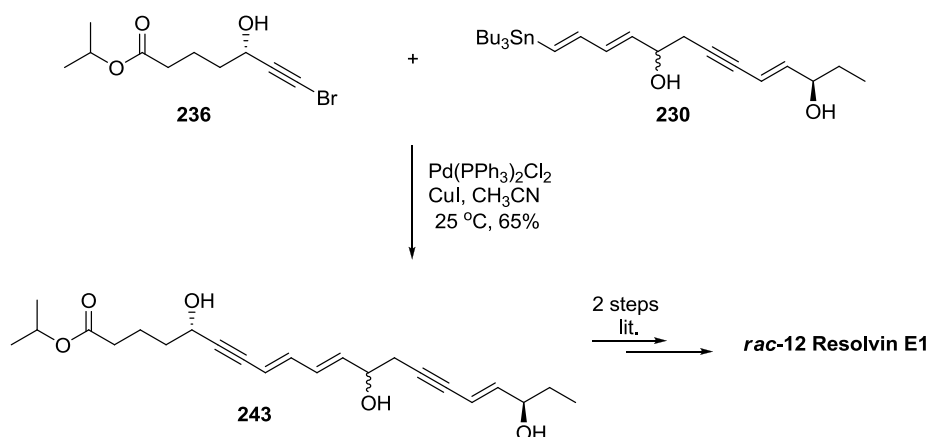


In view of this, compound **122** was segmented into two smaller compounds, propargylmagnesium bromide and the iodide **28**. The latter compound was synthesised in 20% yield and 96% *ee* in 7 steps from 1-pentyn-3-ol (Chapter 3). The iodide **28** was a key fragment in the synthesis of benzoeresolvin E1, along with the stannane **209** and the iodide **197**. From these compounds, the lithium carboxylate salt of benzoeresolvin E1 was prepared in 6 steps (Chapter 4). The key step in the synthesis was a chemoselective sequential Sonogashira-Stille coupling reaction.

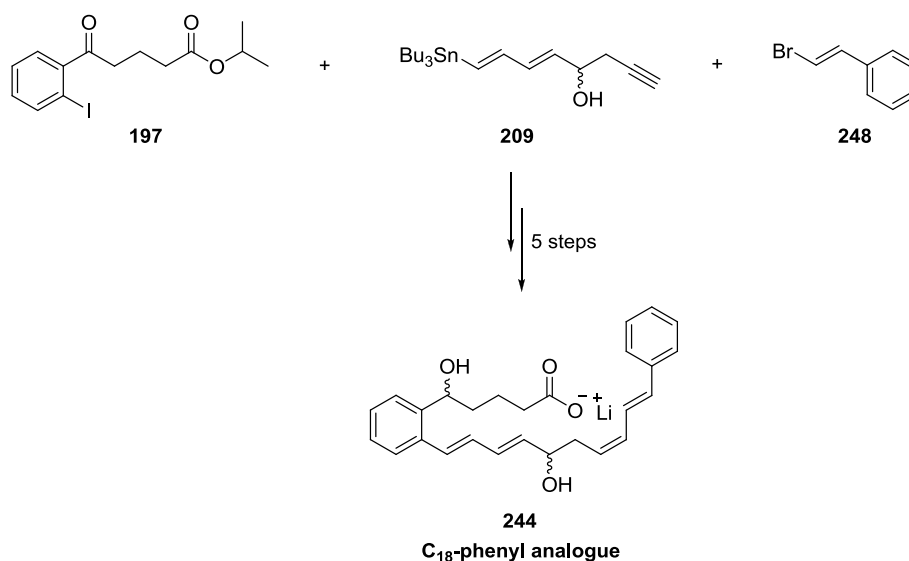


Having synthesised the lithium carboxylate salt of benzoeresolvin E1, the chemical stability of this compound was investigated. A ^1H NMR study conducted at room temperature showed no change to the target compound over 4 days. In comparison, resolvin E1 is known to degrade over the same period of time. This suggests that the benzene ring was significant in improving the stability of resolvin E1 (Chapter 4). *In vitro* studies also showed benzoeresolvin E1 binds to the BLT-1 receptor with an inhibitory constant of $1.05\ \mu\text{M}$. This is comparable to the BLT-1 antagonist SC-41930 that has a K_i of $1.00\ \mu\text{M}$ but is higher than the inhibitory constant of resolvin E1 ($K_i = 70\ \text{nM}$). Thus, the fusion of the benzene ring weakens but retains the binding towards the BLT-1 receptor.

Using the same convergent strategy, the formal total synthesis of *rac*-12 resolvin E1 was completed (Chapter 5). A Stille reaction between compounds 236 and 230 afforded compound 243 in 65% yield. The product intersects the total synthesis of resolvin E1 developed by Allard and was only 2 steps from the target compound.



A C₁₈-phenyl analogue of benzoiresolvin E1 was also prepared (Chapter 6). Replacing the (18*R*)-alcohol with a phenyl ring would simplify the synthesis of the target compound. Using the same convergent approach, the phenyl analogue **244** was synthesised in 5 steps from the key intermediates **197**, **209** and **248**. *In vitro* studies showed that the phenyl analogue **244** binds to the BLT-1 receptor with 68% activity at 10 μ M. This is only slightly lower than the activity of benzoiresolvin E1 (76%), suggesting that the C₁₈-phenyl substituent does not significantly reduce the binding affinity of the molecule.



The final chapter details investigations towards a benzene annulated analogue of leukotriene B₄, named benzoleukotriene B₄. Using the cross-coupling approach developed for benzoiresolvin E1, the key fragment **275** was prepared in 3 steps as an inseparable mixture with the allene **279** (Chapter 7). Alternate methods to synthesis compound **275** using an organolithium and epoxide strategy were investigated, however these were unsuccessful.

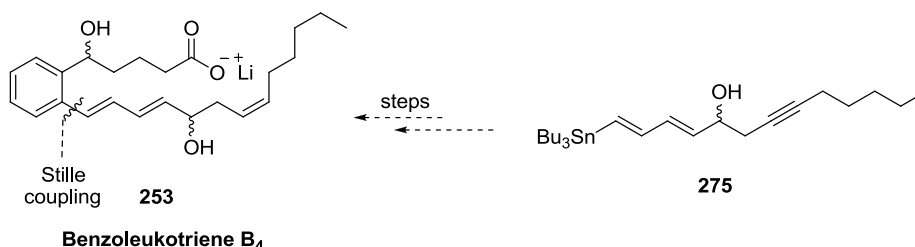


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List of Abbreviations

AIBN	2,2'-Azobis(2-methylpropionitrile)
anh	Anhydrous
ASAP	Atmospheric solids analysis probe
BHT	2,6-Di-tert-butyl-4-methylphenol
Bn	Benzyl
br	Broad
brsm	Based on recovered starting material
cat	Catalytic
CBS	Corey-Bakshi-Shibata catalyst
COSY	Correlation spectroscopy
COX	Cyclooxygenase
CSA	CSA
d	Doublet
DCE	Dichloroethane
DCM	Dichloromethane
DHA	Docosaehaenoic acid
DIBAL	Diisobutylaluminium hydride
DMA	Dimethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	<i>N,N</i> -Dimethylformamide
DMP	Dess-Martin periodinane
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
EDA	1,2-Ethylenediamine
<i>ee</i>	Enantiomeric excess
eq	Equivalents
EPA	Eicosapentaenoic acid

ESI	Electrospray ionisation
Et ₂ O	Ethyl ether
EtOH	Ethanol
g	Grams
GI	Gastro-intestinal
GPCR	G protein-coupled receptor
HMBC	Heteronuclear multiple bond correlation
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IL	Interleukin
<i>i</i> -PrOH	Isopropyl alcohol
L	Litres
LDA	Lithium diisopropylamide
LOX	Lipoxygenase
LRMS	Low resolution mass spectrometry
M	Molar
<i>m/z</i>	Mass to charge ratio
m	Multiplet
MeOH	Methanol
mg	Milligrams
MHz	Megahertz
mL	Millilitres
mmol	Millimoles
mol	Moles
MVK	Methyl vinyl ketone

<i>n</i> -BuLi	<i>n</i> -Butyllithium
NBS	<i>N</i> -bromosuccinimide
NFκ-B	Nuclear transcription factor B
NSAID	Non-steriodal anti-inflammatory drug
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser enhancement spectroscopy
PA ₂	Phospholipase A ₂
PG	Prostaglandin
PMB	<i>p</i> -Methoxybenzyl
PPh ₃	Triphenylphosphine
ppm	parts per million
Pt(dvds)	Karstedt's catalyst
PUFAs	Polyunsaturated fatty acids
q	Quartet
rac	Racemic
rt	Room temperature
s	Singlet
sp	Septet
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBAHS	Tetrabutylammonium hydrogensulfate
TBHP	<i>t</i> -Butyl hydroperoxide
TBDPS	<i>t</i> -Butyldiphenylsilyl
TBS	<i>t</i> -Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TPAP	Tetrapropylammonium perruthenate
w/v	Weight per volume

Chapter 1

Introduction

1.1 Inflammation

Inflammation is ubiquitous in society. It is the body's response to tissue injury or infection and serves to provide a suitable environment to repair the damaged site. This often results in redness, swelling, pain and loss of mobility of the infected area.¹ If left unresolved, it can lead to chronic inflammation. Many ailments such as rheumatoid arthritis,²⁻³ asthma,⁴ diabetes,⁵ periodontal disease,⁶⁻⁷ cardiovascular disease⁸ and Crohn's disease⁹ along with neurological disorders including Alzheimer's disease,¹⁰ autism¹¹ and Parkinson's disease¹² have been strongly linked to chronic inflammation.

Inflammation can be divided into two distinct categories; initiation and resolution (Figure 1.01). The onset of inflammation is typically caused by tissue trauma or microbial invasion of host cells. Pattern recognition receptors present in the cell identify these inflammatory stimuli, producing a cascade of biological signals that trigger the release of pro-inflammatory messenger molecules.¹³ These molecules establish a protective environment for the inflamed tissue and help extradite foreign microbes. Once this process is complete, pro-resolving lipid mediators are synthesised and released into the cells, ultimately repairing the damaged tissue.¹



Figure 1.01: Inflammation overview.

It has been known for some time that prostanoids play a pivotal role in the initial stages of inflammation.¹⁴⁻¹⁷ Prostanoids aid in accelerating the inflammatory process by increasing pain sensitivity and blood flow to an inflamed tissue.¹⁸⁻¹⁹ Prostanoids are derived from arachidonic acid, which is a constituent of the cellular membrane. Hydrolysis of arachidonic acid from the cellular membrane, by a class of enzymes known as phospholipases (PA₂), leads to its release into cells.²⁰

Once released from the phospholipid membrane, arachidonic acid is rapidly converted into an assortment of cell-specific lipid mediators by cyclooxygenase (COX), lipoxygenase (LOX) and epoxygenase (cytochrome P450) enzymes.²¹⁻²² COX enzymes are responsible for the formation of prostanoids (prostaglandins, prostacyclin and thromboxanes), LOX enzymes convert arachidonic acid into leukotrienes and lipoxins while the P450 pathway leads to the synthesis of epoxyeicosatetraenoic acids (EETs), as shown in Figure 1.02.²²

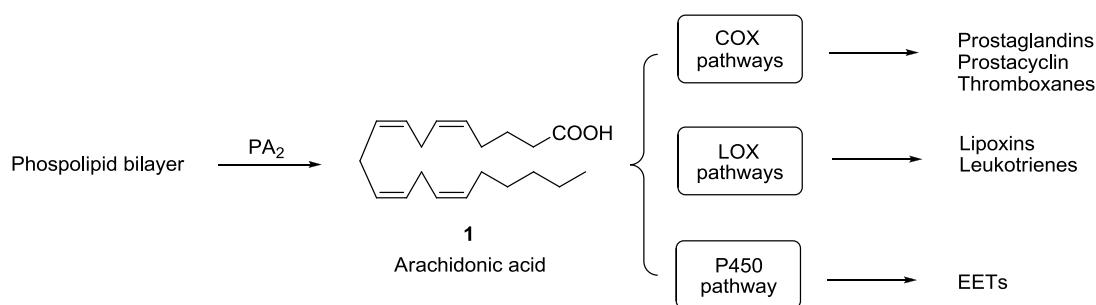


Figure 1.02: Overview of the biosynthetic pathways of arachidonic acid.

1.1.1 Pro-inflammatory lipid mediators

Of the lipid mediators derived from arachidonic acid, the role prostanoids play in inflammation has been extensively documented.²³ Prostanoids encompass a large class of structurally similar compounds that include prostaglandins, prostacyclin and thromboxanes.²⁴ Prostaglandins and prostacyclin contain a cyclopentane ring (red) while thromboxanes can be distinguished by their dioxane moiety (blue).²⁵ The hydroxyl group (purple) at the C₁₂ position is a common feature of all three lipid mediators (Figure 1.03).²⁵ Interestingly, prostanoids were given their name in 1935 after they were isolated from the prostates of male sheep.²⁶⁻²⁷

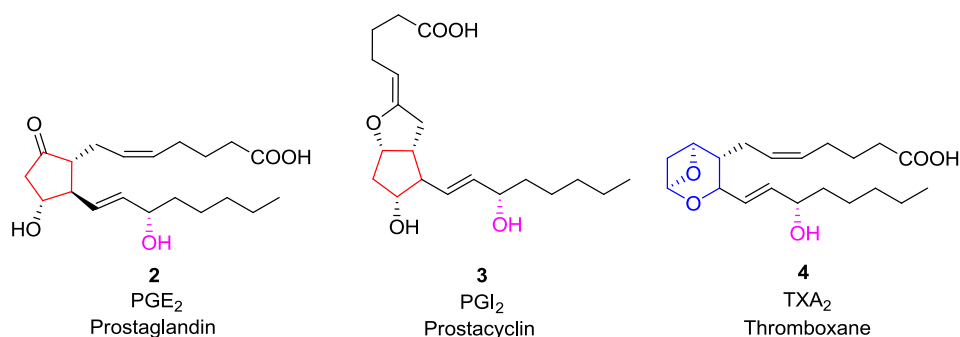


Figure 1.03: Structural comparison of a prostaglandin, prostacyclin and thromboxane.

Prostanoids are biosynthesised by membrane-bound cyclooxygenase (COX) enzymes.²³⁻²⁸ These heme-containing enzymes catalyse the oxygen dependent cyclisation of free arachidonic acid into prostaglandin G₂ (PGG₂) and the peroxidase reduction of PGG₂ into prostaglandin H₂ (PGH₂), as shown in Figure 1.04.²³⁻²⁸ Studies on human tissue isolated from the brain showed two distinct COX isoforms partaking in prostanoid synthesis.²⁹ These were named COX-1 and COX-2. Crystal structures obtained by the Garavito, Browner and Pak groups confirmed the morphology of these enzymes.³⁰⁻³² COX-1 is primarily responsible for the formation of prostanoids during the initial stages of inflammation, with COX-2 up-regulation following several hours later.³³ COX-2 is the major source of prostanoids in inflammation, accounting for over 85% of the prostanoids formed in humans.³⁴⁻³⁵

1.1.2 Biosynthesis of prostanoids

Once PGG₂ is formed, it is converted into a range of prostaglandins that include PGD₂, PGE₂, PGF_{2α}, TxA₂ and PGI₂ (Figure 1.04).²³ The distribution of these prostanoids in the body is dictated by prostanoid synthase enzymes present in different cells and tissues. For example, PGD₂ is predominately expressed in mast cells containing PGD₂ synthase and PGD₂ hematopoietic synthase while PGF_{2α} is synthesised from PGF_{2α} reductase which is located in vascular and uterine smooth muscle cells.^{1,23}

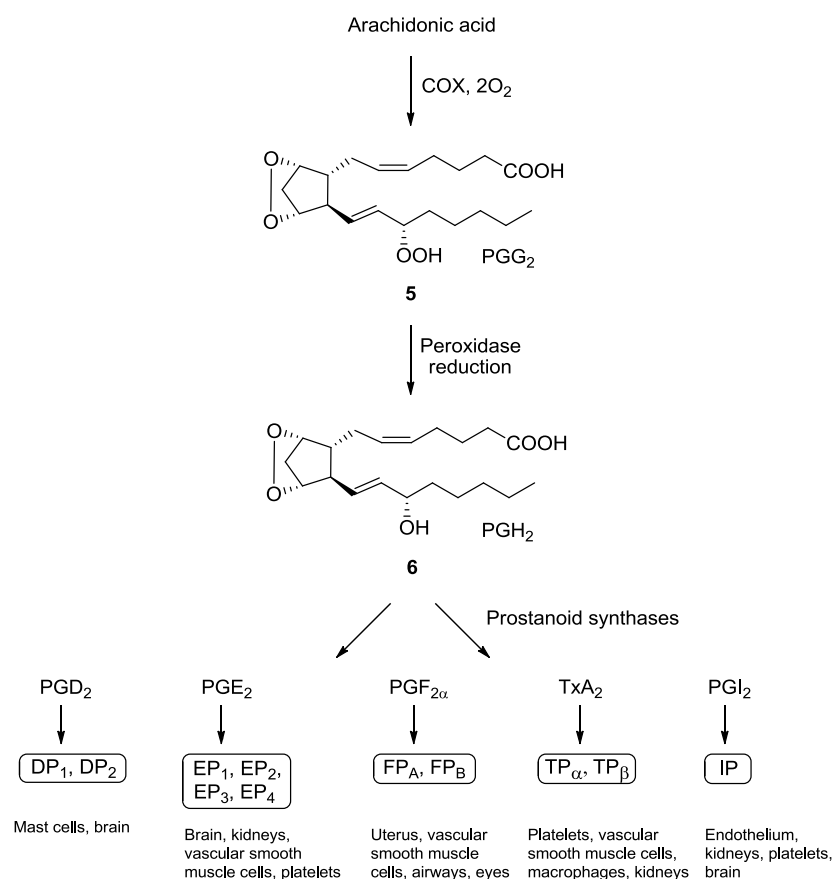


Figure 1.04: Biosynthetic pathway of the prostanoids.³

Upon cellular release, prostanoids interact with G protein-coupled receptors to produce a range of inflammatory responses.³⁶⁻³⁸ The first prostanoid receptor structurally identified was the thromboxane receptor.³⁹ Using the radiolabelled ligand S-145, Ushikubi and co-workers purified the thromboxane receptor from human blood platelets in 1989.³⁹ Two years later, Hirata and co-workers successfully sequenced and cloned this receptor.⁴⁰ This paved the way for the isolation of other prostanoid receptors. By 1995, the receptor for prostacyclin (IP),⁴¹⁻⁴³ two receptors for PGF_{2α} (FP_A and FP_B),⁴⁴⁻⁴⁵ four receptors for PGE₂ (EP₁₋₄)⁴⁶⁻⁴⁹ and two receptors for PGD₂ (DP₁ and DP₂)⁵⁰⁻⁵¹ had been cloned.

1.1.3 Prostanoid actions

PGE₂ and PGI₂ are the main prostanoids involved in inflammation.^{34,38} Both prostanoids contribute to edema formation and leukocyte infiltration.⁵²⁻⁵⁴ This helps maintain a protective environment for the damaged area. PGE₂ and PGI₂ also play a pivotal role in potentiating the pain-producing activity of the nonapeptide

bradykinin, resulting in peripheral sensitisation.⁵⁵⁻⁵⁷ PGD₂ also contributes to inflammation, specifically regulating allergic responses in the lungs.^{27,58} Activation of the DP₁ receptor increases blood flow and vascular permeability while activation of the DP₂ receptor promotes T-cell polarisation.⁵⁹⁻⁶⁰ The latter is essential for triggering the synthesis of a range of cytokines that attract neutrophils to remove pathogens.⁶⁰ Eosinophils are also released during DP₂ stimulation, providing yet another alternative for pathogen extermination.³⁷⁻³⁸ Finally, thromboxanes play a role in inflammation by causing platelet aggregation and regulating the constriction of blood vessels.^{40,61-63}

Since the discovery of prostanoids and their target receptors, three main classes of drugs have been developed to treat the initial stages of inflammation. These include selective prostanoid (PG) antagonists, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.⁶⁴⁻⁶⁷ Each class attenuates inflammation at different stages of the inflammatory pathway (Figure 1.05). PG antagonists function by inhibiting prostanoid specific receptors while cyclooxygenase (COX) inhibitors and corticosteroids prevent the synthesis of prostanoids altogether. The most common approach to treat the onset of inflammation involves NSAIDs and corticosteroids.

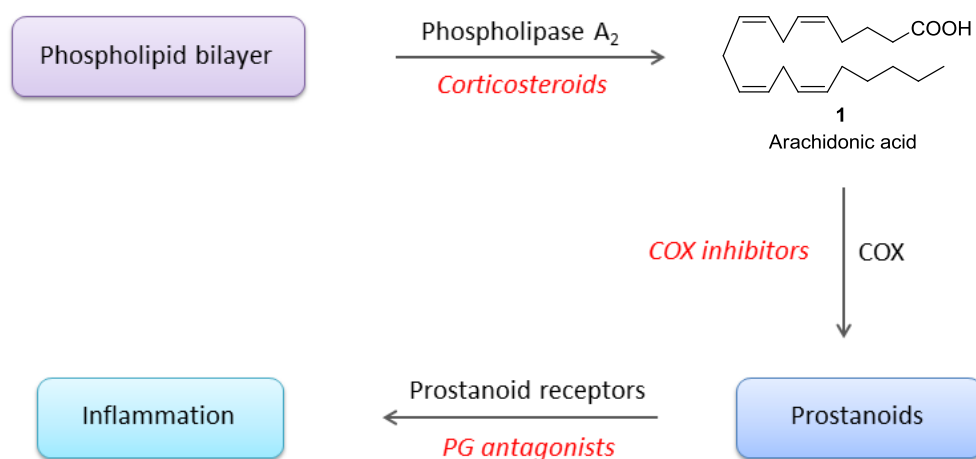


Figure 1.05: Treatment methods for the onset of inflammation.

1.2 Treatment methods for the onset of inflammation

1.2.1 Prostanoid receptor antagonists

Prostanoid receptor antagonists provide targeted treatment for the onset of inflammation.⁶⁸⁻⁷⁰ Unlike COX inhibitors that broadly suppress all prostanoid pathways, prostanoid antagonists selectively inhibit individual receptors.⁷¹ In this way, specific inflammatory responses can be suppressed. Substantial progress in the development of prostanoid antagonists was made following the cloning of several prostanoid receptors in the early 1990s. Through the use of radio-ligand binding assays, an extensive library of antagonists for the DP₁,⁷²⁻⁷⁵ DP₂,⁷²⁻⁷⁵ EP₁,⁷⁶⁻⁷⁸ EP₄,⁷⁹⁻⁸⁰ TP⁸¹⁻⁸⁴ and IP⁸⁵⁻⁸⁶ receptors was rapidly developed while antagonists selective for the FP,⁸⁷⁻⁸⁸ EP₂⁸⁹ and EP₃⁹⁰⁻⁹¹ receptors were slower to emerge. A perceived lack of therapeutic utility and minimal commercial support are reasons for the under-development of the latter class of antagonists.⁶¹

Commercial prostanoid antagonists are typically acyl-sulfonamides. These compounds offer a number of advantages including excellent bioavailability, improved metabolic stability and cheap syntheses.⁶¹ One of the most widely marketed sulfonamide containing prostanoid antagonist is Ramatroban[®].⁹² Developed by the German company Bayer, Ramatroban[®] is a potent dual acting thromboxane and PGD₂ antagonist.⁹² It is used in the treatment of cardiovascular diseases and allergic rhinitis.⁹³⁻⁹⁵ By targeting the thromboxane receptor, key inflammatory processes such as vascular permeability and platelet aggregation are mitigated (Figure 1.06).⁹⁶⁻⁹⁷ Ramatroban[®] also inhibits the PGD₂ receptor expressed in pro-inflammatory mast cells.⁹² This attenuates leukocyte infiltration and degranulation of granulocytes by suppressing the monocyte chemoattractant protein MCP-1, preventing exacerbation of late-phase inflammation.⁹² Studies by Ishizuka and co-workers also showed that Ramatroban[®] can prevent the build up of scar tissue sustained from soft-tissue injuries.⁹⁸

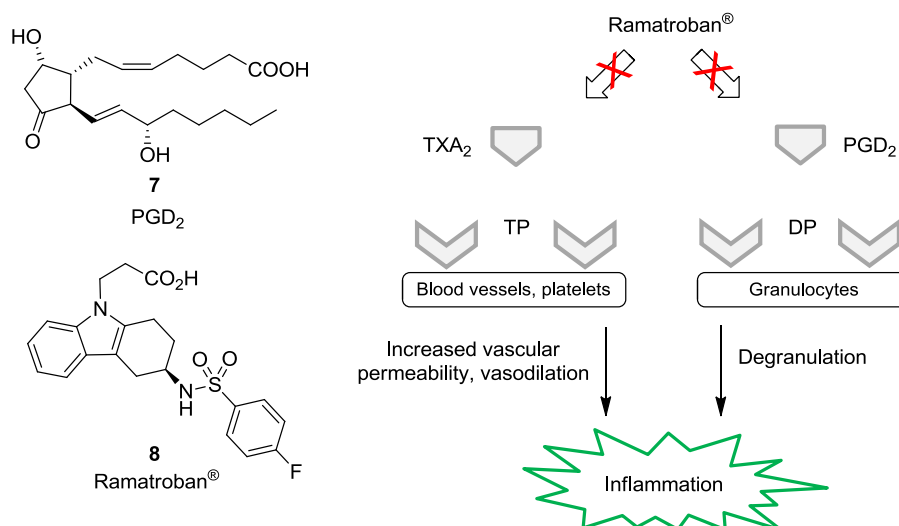


Figure 1.06: Mechanism of action of Ramatroban[®]

Despite the availability of potent and selective antagonist for most of the prostanoid receptors, their future as a treatment for inflammation is not encouraging. Although some prostanoid antagonists such as Ramatroban[®], Domitroban[®], Ifetroban[®] and Terutroban[®] have received regulatory approval to be marketed, these cases are limited and are confined to a select number of countries.⁹² In the last decade, an increasing number of these antagonists have been discontinued by pharmaceutical companies. Prostanoid antagonists appear to be superseded by more effective treatments such as NSAIDs, corticosteroids and resolution phase drugs. Expectations that one prostanoid and one receptor play a dominant role in diseases induced by inflammation are extremely lofty. Instead, it is believed that a number of prostanoids act together to initiate and sustain diseases.¹ With the exception of several dual acting compounds, it appears that the majority of prostanoid antagonists on the market will be replaced over the coming years with other treatments.⁹²

1.2.2 Non-steroidal anti-inflammatory drugs

In recent times, NSAIDs have become the main treatment for inflammation.⁹⁹ Since the turn of the twentieth century, the number of NSAIDs available to patients has grown significantly, with over fifty different NSAIDs currently on the global market.¹ Unlike prostanoid antagonists that inhibit prostanoid receptors, the majority of NSAIDs target a different class of enzymes known as cyclo-oxygenases (COX). By inhibiting the COX enzymes, free arachidonic acid is unable to be converted into

prostanoids, thus terminating inflammation in the initial stages.¹⁰⁰ In the early 1970s, Vane was the first to elucidate the anti-inflammatory properties of several commonly used NSAIDs including indomethacin and aspirin (Figure 1.07).¹⁰¹ Using assays containing Krebs solution, Vane observed a 47% reduction in $\text{PGF}_{2\alpha}$ activity when rabbits were administered with indomethacin at a concentration of $0.75\ \mu\text{M}$ while a 24% reduction with aspirin was observed at $35\ \mu\text{M}$.¹⁰⁰ Since this research, many studies have investigated the anti-inflammatory properties of a range of other NSAIDs.¹⁰²⁻¹⁰⁵

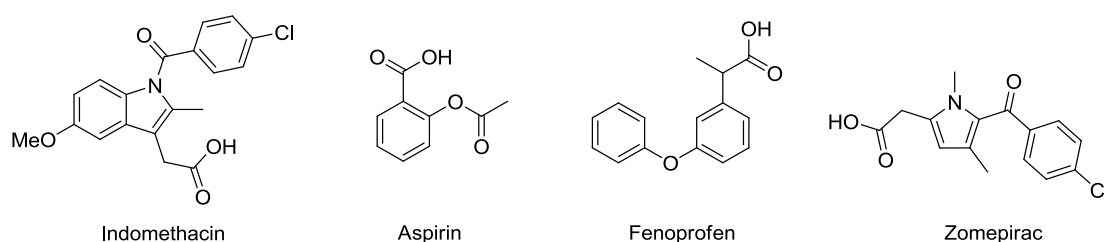


Figure 1.07: Commonly marketed NSAIDs for the treatment of inflammation.

Traditional NSAIDs such as fenopropfen and zomepirac inhibit both the COX-1 and COX-2 enzymes (Figure 1.07).¹⁰⁶ Although effective towards treating symptoms of inflammation, these compounds can cause a wide range of side effects that include diarrhoea, abdominal pain, nausea, gastric ulcers, bone marrow disturbances, liver disorders and renal impairment.¹⁰⁷⁻¹¹⁰ It is estimated that 34–46% of traditional NSAID users sustain gastrointestinal (GI) damage, with up to 4,500 hospital admissions and 400 deaths recorded each year in Australia.¹¹¹ A range of histological studies have linked these side effects to the COX-1 enzyme.¹¹²⁻¹¹⁴ COX-1 is responsible for regulating the GI tract by stimulating bicarbonate secretion and reducing acid excretion.¹¹⁵ Disruptions to these functions arise upon NSAID binding, causing GI related side effects.¹⁰⁵ These studies have paved the way for the development of NSAIDs selective for the COX-2 enzyme. It was anticipated that COX-2 selective inhibitors would be superior to traditional nonselective NSAIDs as they could reduce inflammation without interfering with the GI-protective functions of COX-1.^{106,116}

Early attempts to develop selective COX-2 inhibitors led to the synthesis of NS-398 and DuP-697 (Figure 1.08).¹¹⁶⁻¹¹⁷ These drugs have served as the platform for the development of two main classes of COX-2 inhibitors; the sulides and the

coxibs.¹¹⁸⁻¹¹⁹ Marketed drugs from these classes include nimesulfide (Nimalox[®]), rofecoxib (Vioxx[®]), celecoxib (Celebrex[®]), valdecoxib (Bextra[®]) and etoricoxib (Arcoxia[®]).

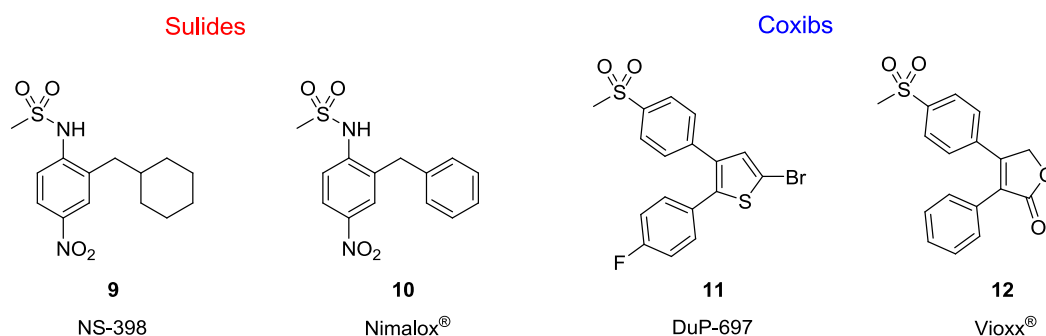


Figure 1.08: The sulides and the coxibs.

A comparative study by Warner et al. showed sulides and coxibs to be up to fifty-times more selective for COX-2 than non-selective NSAIDs such as fenoprofen and zomepirac (Figure 1.09).¹²⁰ Unlike traditional NSAIDs, these drugs are bulkier and cannot fit into the COX-1 receptor. This is attributed to the bulky amino acid isoleucine present at the active site of COX-1 which restricts the access of large, rigid compounds.¹ On the contrary, the COX-2 enzyme has a valine amino acid. This is smaller than isoleucine, providing a larger pocket for molecules to fit in the active site. As such, COX-2 can accommodate bulkier compounds than COX-1.¹

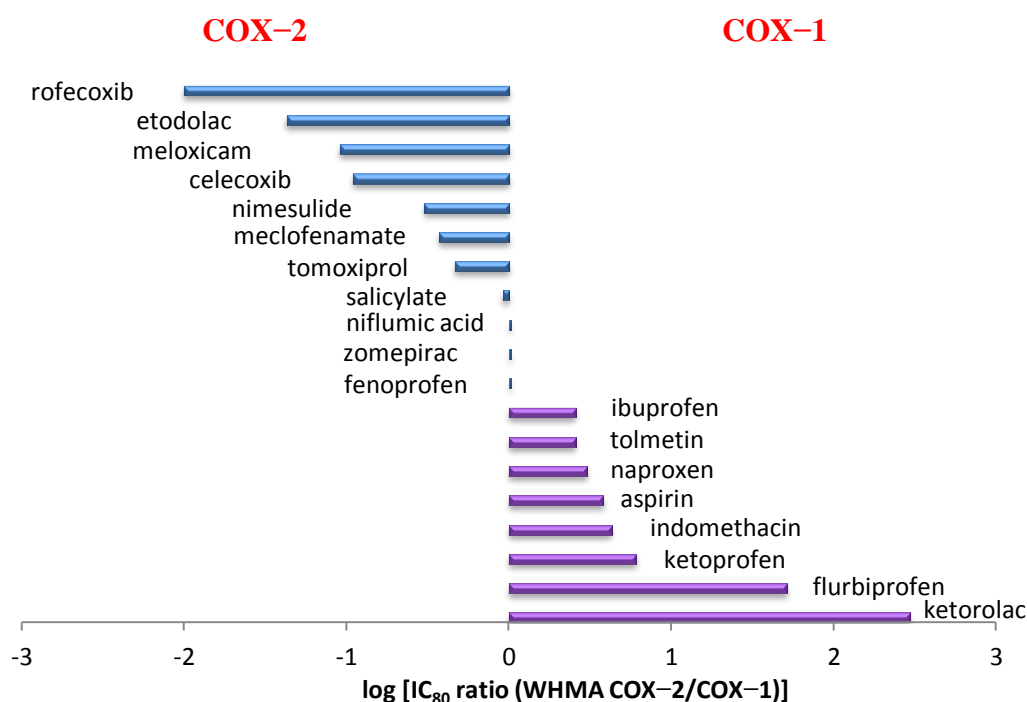


Figure 1.09: Selectivity of NSAIDs given as log inhibitory concentrations (IC₈₀).¹²⁰

Despite their effectiveness as potent anti-inflammatory drugs, chronic use of selective COX-2 inhibitors can lead to cardiovascular problems.¹²¹ A study conducted by Bombardier and co-workers in 2000 showed an increased risk of myocardial infarction in elderly patients consuming rofecoxib (Vioxx®) over an eleven month period.⁹⁹ This was a four-fold increase compared to individuals who were given the non-selective NSAID naproxen.⁹⁹ Further studies by Aw and co-workers showed a 61% risk of developing hypertension and elevated blood pressure in patients administered with celecoxib, rofecoxib or etoricoxib.¹²² Coxib induced suppression of PGI₂ followed by accelerated atherosclerosis have been linked to these cardiovascular effects.¹²³ In light of these findings, Vioxx® was voluntarily withdrawn from the market by Merck in 2004, followed by the withdrawal of Bextra® (valdecoxib) by Pfizer in 2005.¹²³ Consequently, the future of selective COX-2 inhibitors for the treatment of inflammation appears ambiguous at best.

1.2.3 Corticosteroids

Corticosteroids have been known since the early 1950s to exhibit anti-inflammatory properties.¹²⁴ Along with NSAIDs, they are among the most widely used anti-inflammatory drugs in the world. Many inflammatory related conditions such as

ulcerative colitis,¹²⁵ rheumatoid arthritis,¹²⁶ Crohn's disease¹²⁷ and asthma¹²⁸ are treated using corticosteroid therapy. Corticosteroids are divided into two distinct groups; mineralocorticoids and glucocorticoids (Figure 1.10).¹²⁹⁻¹³⁰

Mineralocorticoids regulate the body's blood pressure by increasing sodium and water retention in the kidneys while glucocorticoids mitigate inflammation by regulating pro-inflammatory transduction pathways.¹²⁹ Both classes are endogenously produced in the adrenal cortex from cholesterol. Extensive efforts have been made over the last three decades to design drugs that mimic glucocorticoids synthesised in the body.^{129,131} More than 300 glucocorticoids are marketed world-wide, with the three drugs Flixotide[®], Nasonex[®] and Pulmicort[®] accounting for over 50% of corticosteroid sales in 2011.¹³⁰

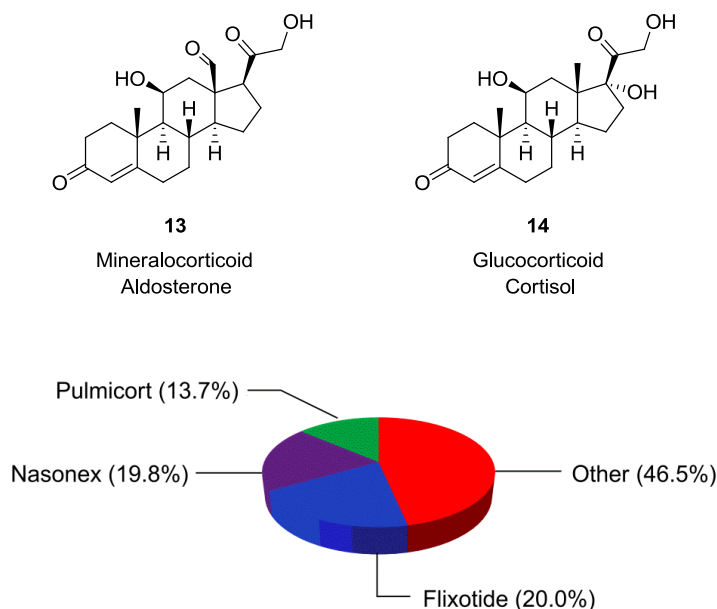


Figure 1.10: Top three marketed glucocorticoids in 2011.¹³⁴

Glucocorticoids function by regulating multiple inflammatory genes that are activated during inflammation.¹³² As much as 1% of a cells total genome is altered in this way.¹³³ Glucocorticoids exert anti-inflammatory action through a series of complex biological pathways. They firstly diffuse across a cell membrane and bind to glucocorticoid receptors (GR) located in the cytoplasm. These receptors are typically bound to molecular chaperones such as heat shock protein-90 or FK-binding protein.¹³² Molecular chaperones serve as GR protection, preventing unwanted nuclear localisation from occurring.¹³⁴⁻¹³⁵ Once the glucocorticoid has

bound to the GR, conformational changes are induced in the complex. This causes the molecular chaperone to dissociate, with the complex translocating into the nucleus.¹³²

The glucocorticoid-GR complex then binds to specific glucocorticoid-responsive genes located in the promoter region of DNA. With the assistance of co-activator molecules such as CBP, pCAF or GRIP-1, acetylation of histone lysine groups trigger the unravelling of chromatin.¹³⁶⁻¹³⁷ This open chromatin structure facilitates RNA polymerase II binding which initiates the transcription of genes encoded for anti-inflammatory inhibitor proteins. These include lipocortins, SLPI, IL-10 and the inhibitor of NFκ-B, IκB-α.¹³² In this way, corticosteroids are different from NSAIDs and prostanoid antagonist as they reduce inflammation through a multitude of transduction pathways.

One of the most widely documented class of glucocorticoid induced proteins are lipocortins.¹³³ Lipocortins are localised cellular proteins that prevent the formation of free arachidonic acid.⁶⁴ Originally isolated from guinea pig macrophages by Blackwell and co-workers in 1980, over fifteen different lipocortin proteins have been discovered in humans.¹³⁸⁻¹⁴⁰ These variants are the consequence of cellular proteolysis and are shown in several studies to exhibit similar functional activities.¹⁴¹⁻¹⁴³ Lipocortins reduce inflammation by mitigating the activity of the phospholipase A₂ enzyme (PA₂).^{133,144} Key studies conducted by Hirata and Schlaepfer suggest that lipocortins reduce phospholipase activity through calcium sequestration.¹⁴⁴⁻¹⁴⁵ By forming a ternary complex with Ca²⁺ and the phospholipid membrane, lipocortins deprive PA₂ of calcium, which is an essential component for cellular phospholipid hydrolysis.¹⁴⁴⁻¹⁴⁵

Despite the treatment of many diseases and disorders, corticosteroids are known to cause severe side effects when used over a prolonged period of time. These include hyperglycemia,¹⁴⁶ insulin resistance,¹⁴⁶ osteoporosis,¹⁴⁷ depression,¹⁴⁸ skin fragility¹³² and growth retardation.¹³² Although little is known about the cause of these side effects, it is speculated that corticosteroid induced suppression of genes coding for bone metabolism, skin structure and the hypothalamo-pituitary axis are responsible for these effects.¹⁴⁹

1.3 Treatment methods for the resolution of inflammation

An alternative approach to reduce inflammation in the body is to mimic the protectin and resolvins messenger molecules. These messenger molecules are endogenously synthesised during the resolution phase of inflammation. They are derived from omega-3 polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and α -linoleic acid and are ultimately introduced in our diet from fish oil, krill oil, linseed and an assortment of other supplements.¹⁵⁰⁻¹⁵⁵

1.3.1 Omega-3 polyunsaturated fatty acids

The benefits of omega-3 fatty acids in human health have been known for nearly a century. George and Mildred Burr were the first to demonstrate the importance of PUFA enriched diets.¹⁵⁹⁻¹⁶⁰ They showed a compelling link between the health of laboratory rats and the exclusion of fat-free diets. In most cases, failure of the kidneys, bladder and physiological deterioration were noted, with premature death a definite outcome.¹⁵⁶⁻¹⁵⁷ Despite these findings, the importance of PUFAs went largely unnoticed until research conducted by Bang et al. in the early 1970s.¹⁵⁸ By comparing the dietary intake of Greenland Eskimos and Caucasian Danes, they were able to show the benefits of omega-3 rich diets towards minimising chronic inflammatory diseases. Greenland Eskimos who consumed large amounts of whale, seal and fish, had lower incidences of cardio-vascular disease and arthritis.¹⁵⁹⁻¹⁶⁰

Since this research, numerous studies have uncovered an assortment of other benefits of omega-3 rich diets including a lower risk of developing cancer, type-2 diabetes, autoimmune diseases, rheumatoid arthritis, cardiovascular diseases, immunomodulation and Alzheimer's disease.¹⁶¹⁻¹⁶⁶ Recent findings by Mozaffarian have also shown a remarkable 27% reduction in the mortality of individuals who have PUFA rich diets compared to those with a low omega-3 fatty acid intake. This equates to an extended life expectancy of up to 2.2 years.¹⁶⁷ The Australian government has also recognised the unique array of benefits provided by PUFAs and the seriousness of their deficiencies, with recommended daily intakes made available to the community.¹⁶⁸

1.3.2 Biosynthesis of resolution phase lipid mediators

Although EPA and DHA were known to be beneficial for human health, the biosynthetic pathways for these properties remained a mystery for many years. Recent research conducted by Serhan and co-workers have discovered the first molecular level evidence for the health promoting contributions of EPA and DHA.¹⁶⁹ By treating mice with PUFAs and aspirin, then subjecting the inflammatory exudates to liquid chromatography-tandem mass spectrometry, they were able to profile the loss or gain of lipid mediators. This study uncovered a new class of bioactive messenger molecules, named the resolvins and protectins, that are responsible for the resolution of inflammation.¹⁶⁹ It was later discovered that E-series resolvins are derived from EPA while DHA is the precursor for the D-series resolvins and protectins (Figure 1.11).¹⁷⁰ The key difference between the two series is the number of carbons and double bonds in the skeletal backbone. E-series resolvins are twenty carbon molecules with five double bonds while D-series resolvins have twenty two carbons and six double bonds.

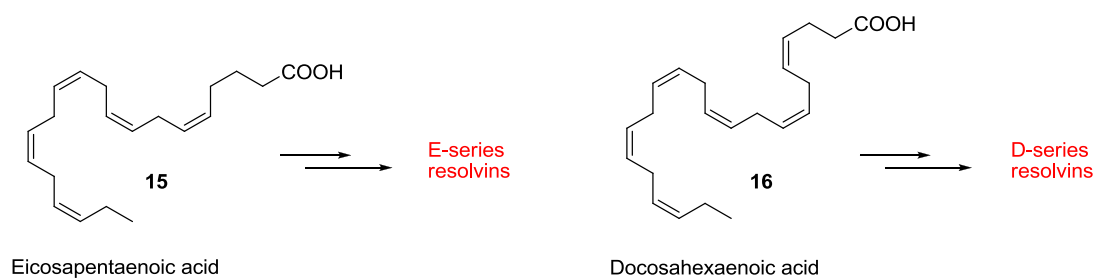
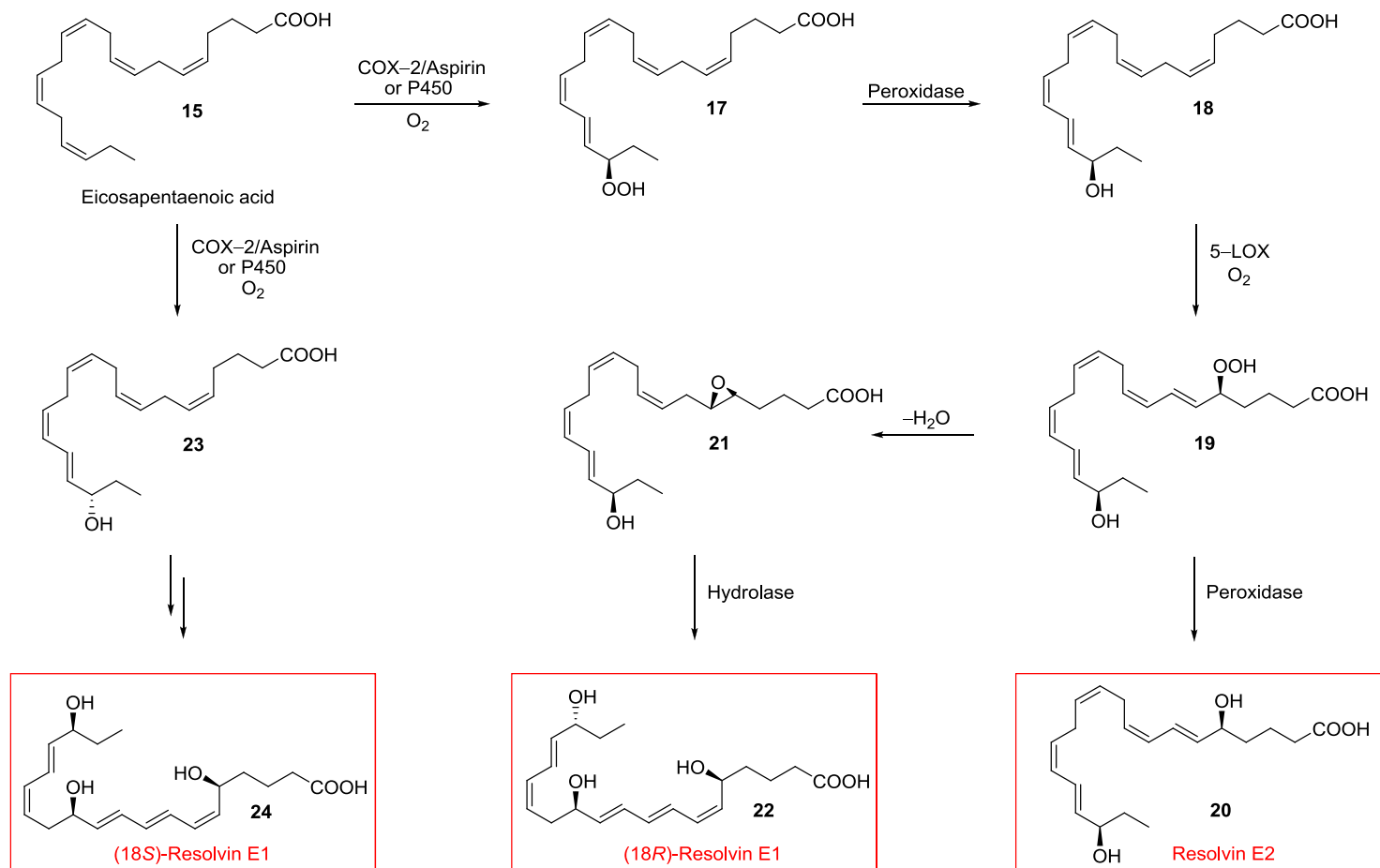


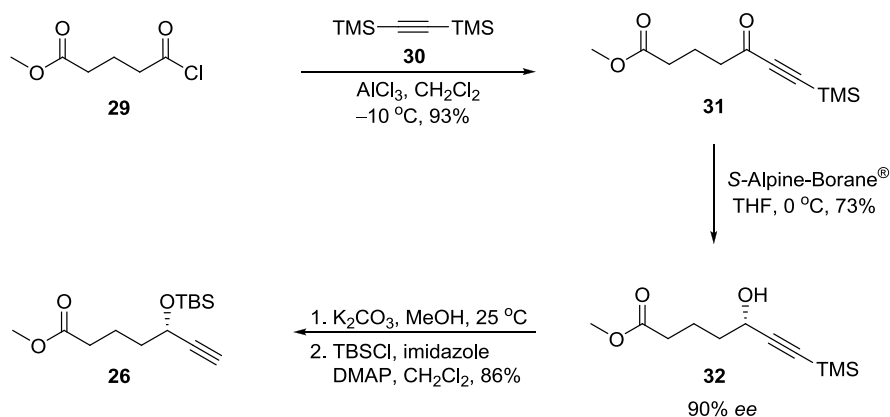
Figure 1.11: EPA and DHA omega-3 fatty acids.

EPA is converted into the pro-resolving messenger molecules resolvins E1 and resolvins E2 via the biosynthetic pathway shown in Scheme 1.01.¹⁵¹ Acetylated COX-2 or cytochrome P450 catalyses the oxygenation of EPA **15**, forming the (18*R*)-peroxide **17** which is reduced to (18*R*)-HEPE **18** via a peroxidase enzyme.¹⁶⁹ A lipoxygenation reaction that is catalysed by the 5-LOX enzyme then forms the peroxide **19** from (18*R*)-HEPE **18**. This intermediate is converted into the epoxide **21** which undergoes enzymatic hydrolysis via a hydrolase enzyme to produce (18*R*)-resolvins E1 **22**. Alternatively, the peroxide **19** can be reduced via a peroxidase enzyme to afford resolvins E2 **20**.¹⁷¹ Recent studies have shown that the (18*S*)-resolvins E1 epimer **24** is also produced via a similar pathway.¹⁷²



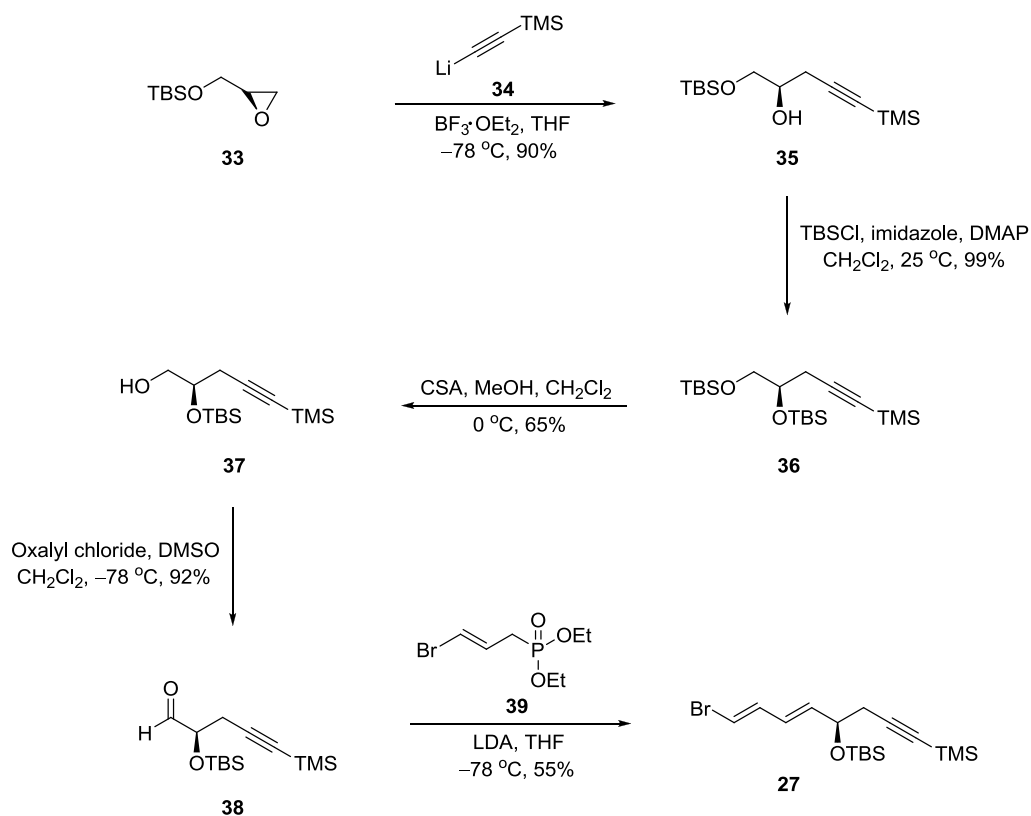
Scheme 1.01: Biosynthetic pathway for the E-series resolvins.¹

The key intermediate **26** was used to form the C₁–C₇ portion of resolvin E1 methyl ester **25**. This compound was synthesised in 4 steps starting from methyl 4-chloroformylbutanoate **29** (Scheme 1.03). The starting material was treated with aluminum chloride and bis(trimethylsilyl)acetylene **30** to afford the ketone **31**. This compound was asymmetrically reduced using *S*-Alpine-Borane[®] to furnish the (*S*)-enantiomer of alcohol **32** in 73% yield and 90% *ee*. The TMS group was removed using potassium carbonate in methanol followed by protection of the alcohol with a TBS group to afford the intermediate **26**.



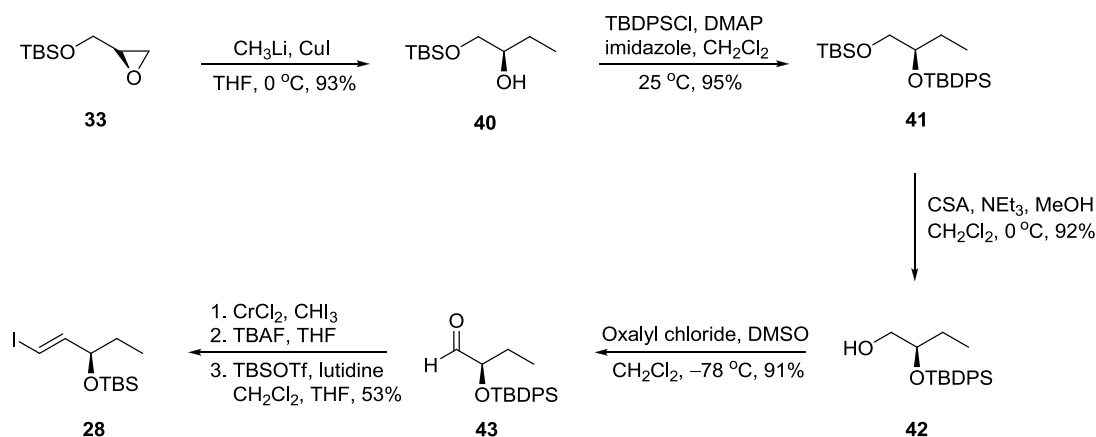
Scheme 1.03: Preparation of the ester **26**.¹⁸⁰

The starting point for the synthesis of the intermediate **27** was the TBS protected chiral glycidol **33** (Scheme 1.04). The addition of the organolithium reagent **34** to this compound gave the alkylated product **35**. Compound **35** was protected with a TBS group, giving the disilylated compound **36** in 99% yield. Selective deprotection of the primary alcohol using CSA followed by a Swern oxidation afforded the aldehyde **38** in 60% yield in 2 steps. A Horner-Wadsworth-Emmons olefination between the aldehyde **38** and compound **39** then furnished the key intermediate **27**.



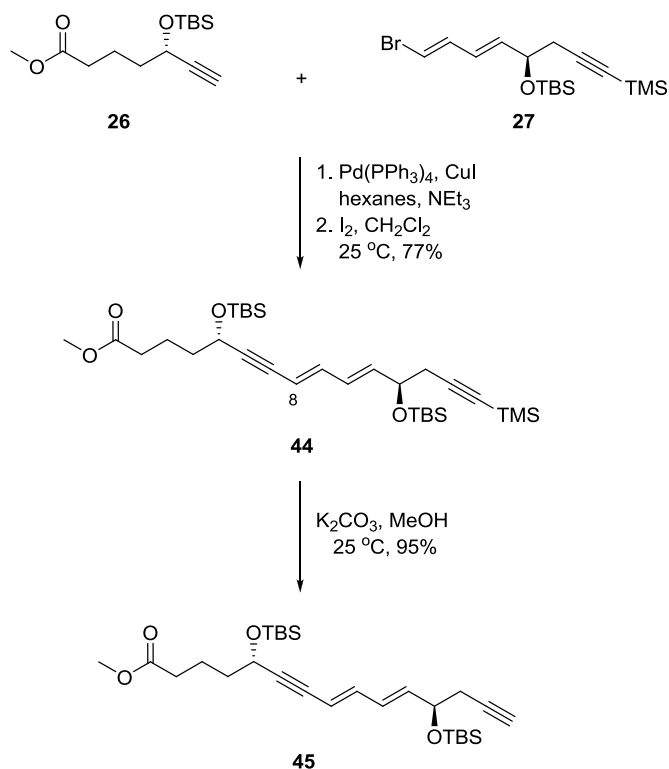
Scheme 1.04: Preparation of the bromide **27**.¹⁸⁰

The intermediate **28** was used to form the C₁₆–C₂₀ portion of resolvins E1 methyl ester **25**. Using the same starting material as in Scheme 1.04, the iodide **28** was synthesised in 7 steps (Scheme 1.05). Alkylation of glycidol **33** using methyllithium followed by protection of the secondary alcohol with a TBDPS group afforded compound **41**. Selective deprotection of the primary alcohol using CSA followed by oxidation of this functional group gave the aldehyde **43**. This compound was then converted into the iodide **28** in 53% yield over 3 steps. These steps included a Takai olefination using CrCl₂ and iodoform, removal of the TBDPS group and protection of the allylic alcohol with TBS.



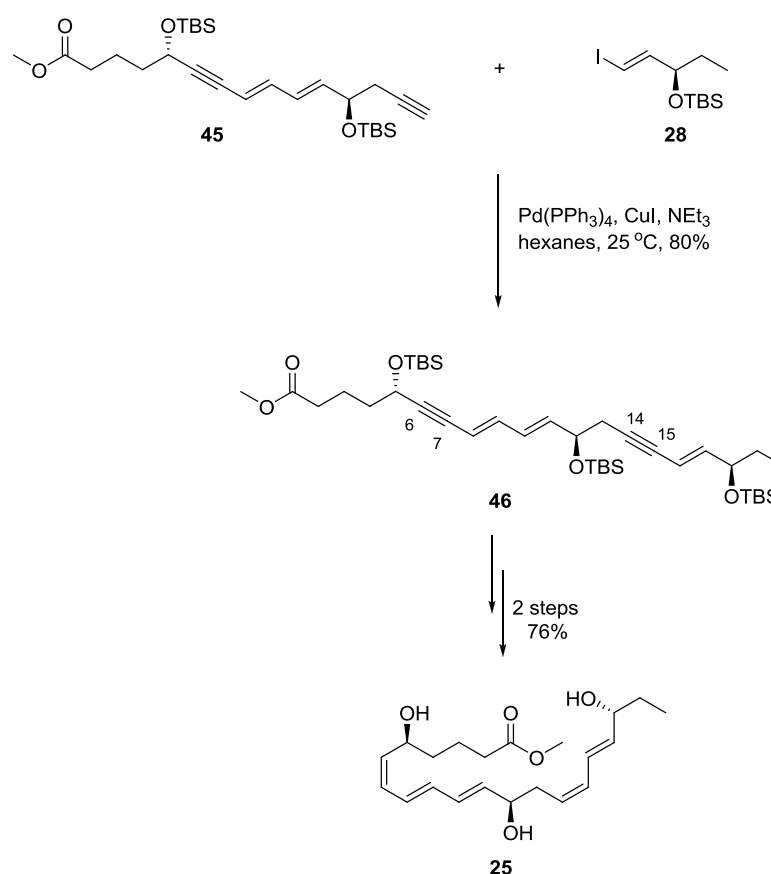
Scheme 1.05: Preparation of the iodide **28**.¹⁸⁰

Having synthesised the key fragments, compounds **26** and **27** were coupled together to afford the Sonogashira product **44** as a mixture of stereoisomers at the C₈ position (Scheme 1.06). Treatment of this compound with a catalytic amount of iodine in dichloromethane gave the desired 8*E*-isomer while the TMS group of compound **44** was removed using Na₂CO₃ to give compound **45**.



Scheme 1.06: Synthesis of compound **45**.¹⁸⁰

The final steps of the synthesis involved a Sonogashira reaction between the alkyne **45** and the iodide **28** (Scheme 1.07). This gave compound **46** in 80% yield as the 16*E*-isomer. The target compound **25** was then prepared in 2 steps from compound **46** by global deprotection of the silyl groups and reduction of the C₆–C₇ and C₁₄–C₁₅ alkynes using a Zn(Cu/Ag) amalgam. The longest linear sequence of compound **25** was 11 steps from glycidol **33** and had an overall yield of 13%.

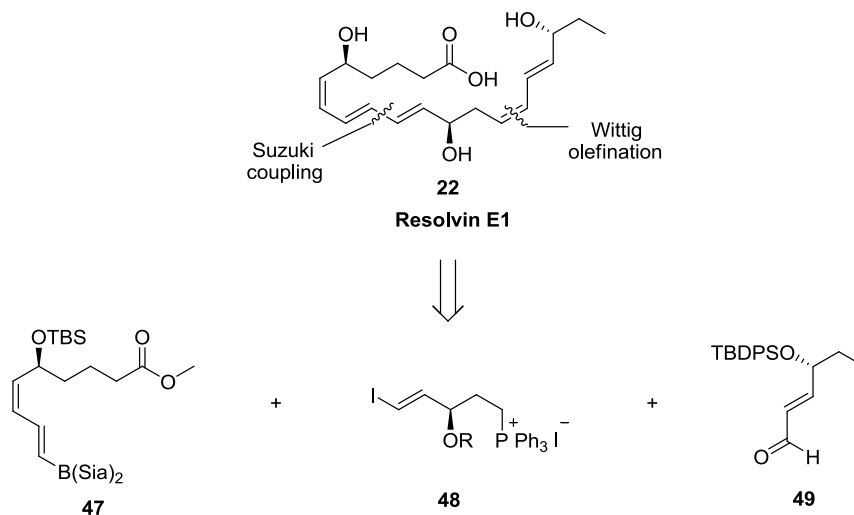


Scheme 1.07: Final steps in the synthesis of resolvin E1 methyl ester **25**.¹⁸⁰

Despite developing the first total synthesis of resolvin E1, Petasis recognised that the enantiomerically pure glycidol **33** was an expensive starting material for compounds **27** and **28** (\$47.50/g, Sigma-Aldrich).¹⁸⁴ Subsequently, the preparation of analogues of resolvin E1 would be costly. Kobayashi and Ogawa addressed this issue in their total synthesis of resolvin E1 by using cheaper starting materials such as propionaldehyde and methyl 5-oxopentanoate.¹⁸¹

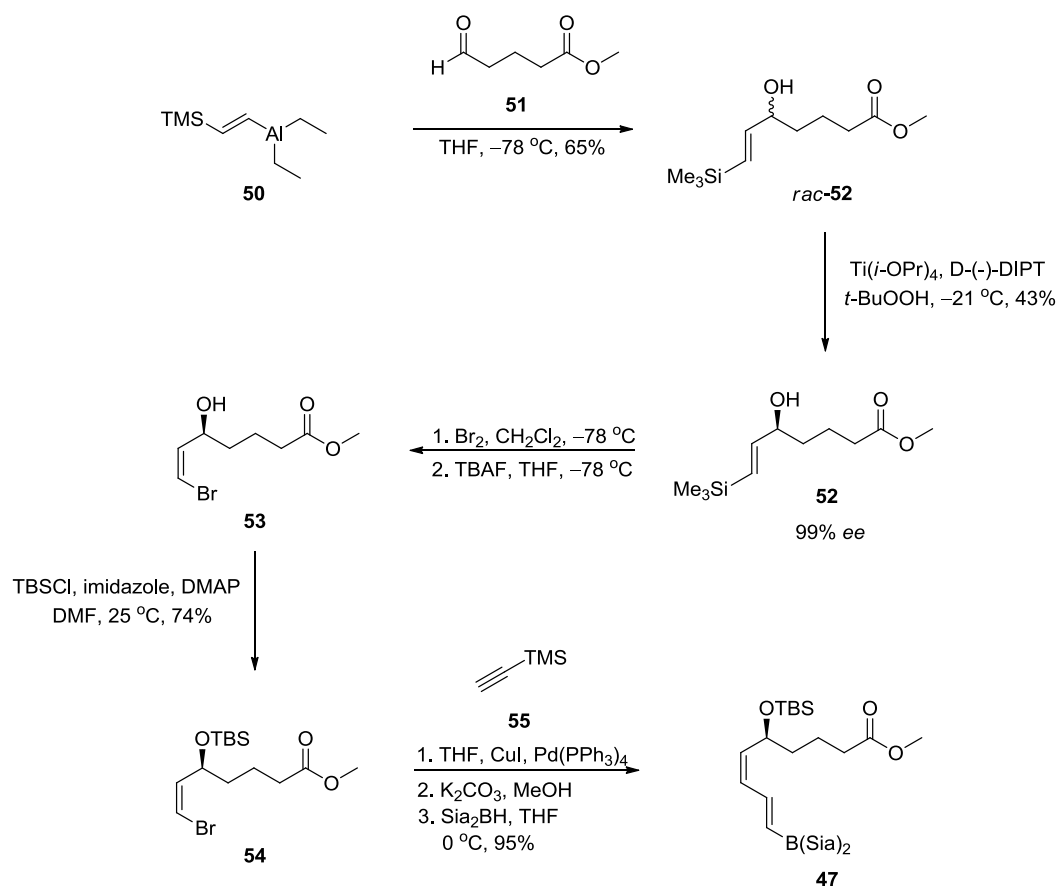
1.4.2 Total synthesis of resolvin E1 developed by Kobayashi

The second total synthesis of resolvin E1 was released by Kobayashi and Ogawa in 2009.¹⁸¹ The linchpin for this synthesis was a Suzuki reaction at the C₉–C₁₀ position and a Wittig olefination at the C₁₄–C₁₅ position (Scheme 1.08). The key intermediates for this synthesis were compounds **47**, **48** and **49**.



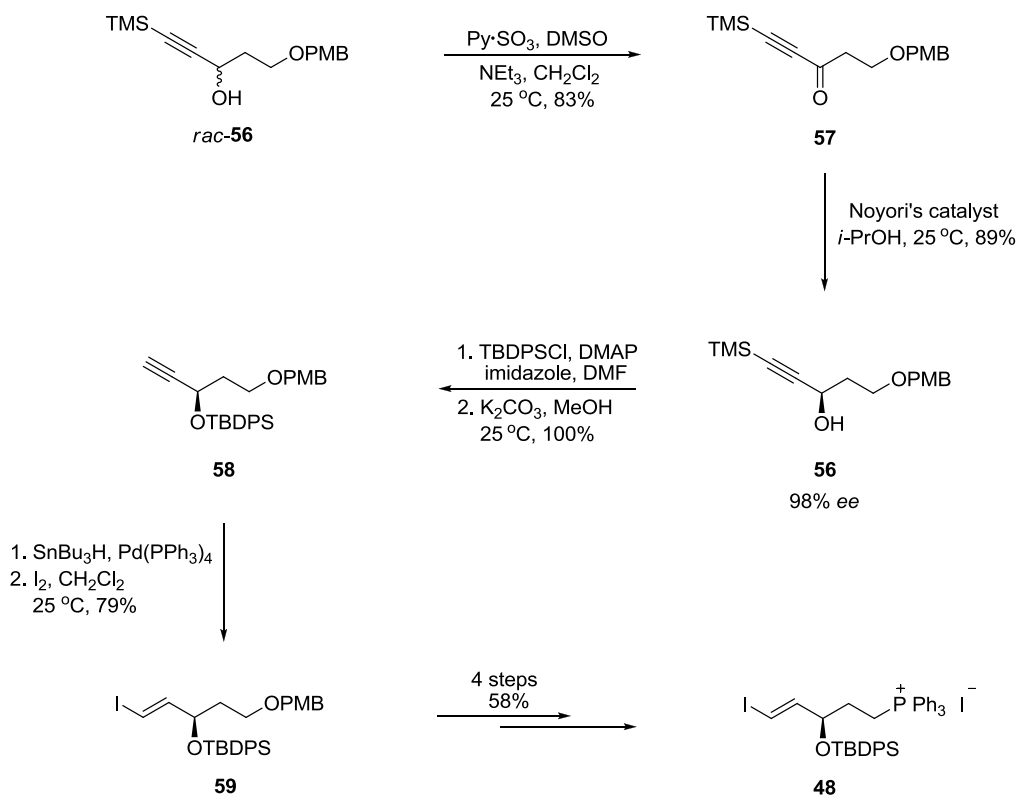
Scheme 1.08: Retrosynthesis of resolvin E1 **22** developed by Kobayashi.¹⁸¹

The intermediate **47** provided access to the C₁–C₉ portion of resolvin E1 **22**. The starting point for this compound was methyl 5-oxopentanoate **51** (Scheme 1.09). Addition of compound **50** to **51** afforded a racemic mixture of the alcohol **52**. Kinetic resolution of the racemic alcohol using Ti(*i*-OPr)₄ and D-(-)-DIPT provided the (*S*)-enantiomer in 43% yield and 99% *ee*. This compound was converted into the bromide **53** in 2 steps followed by protection of the secondary alcohol with a TBS group to afford compound **54** in 74% yield over 3 steps. A Sonogashira reaction between compound **54** and the alkyne **55** followed by removal of the TMS group and reduction of the alkyne with disiamylborane gave the key intermediate **47** in 95% yield over 3 steps.



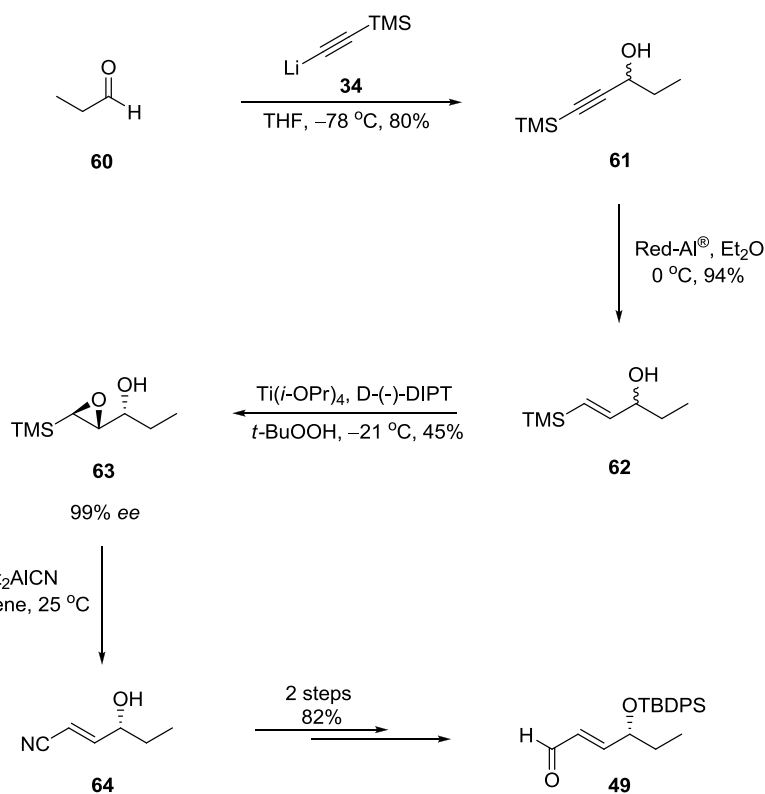
Scheme 1.09: Preparation of the intermediate **47**.¹⁸¹

The intermediate **48** was synthesised in 10 steps starting from compound **56** (Scheme 1.10). The starting material for this synthesis was inturn prepared from 1,3-propanediol in 4 steps and 58% yield.¹⁸¹ A Parikh-Doering oxidation of the alcohol **56** afforded the ketone **57**. The ketone was reduced to the (*R*)-alcohol using Noyori's catalyst, giving compound **56** in 89% yield and 98% *ee*. Subsequent protection of the secondary alcohol with a TBDPS group followed by removal of the TMS group using K_2CO_3 in methanol furnished the alkyne **58**. Hydrostannation of the alkyne and treatment with iodine then afforded compound **59**. Functional group manipulation of compound **59** gave the iodide **48** in 58% yield over 4 steps.



Scheme 1.10: Preparation of the iodide **48**.¹⁸¹

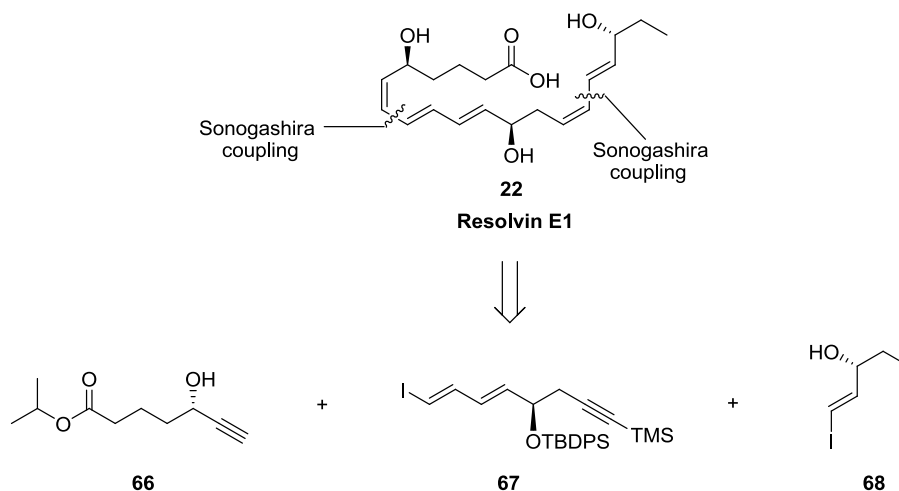
The final intermediate **49** was synthesised via a kinetic resolution strategy starting from propionaldehyde **60** (Scheme 1.11). Treatment of **60** with the lithium acetylide **34** afforded *rac*-alcohol **61**. The alkyne was reduced to an *E*-alkene using Red-Al[®], followed by kinetic resolution of the *rac*-alcohol using D-(-)-DIPT and Ti(*i*-OPr)₄ to give the epoxide **63** in 45% yield and 99% *ee*. Epoxide ring opening was then achieved with diethylaluminium cyanide, affording compound **64** after elimination of the alcohol and TMS group. The secondary alcohol was protected with a TBDPS group and the nitrile moiety was reduced to an aldehyde using DIBAL, giving compound **49** in 82% yield from the epoxide **63**.



Scheme 1.11: Synthesis of the aldehyde **49**.¹⁸¹

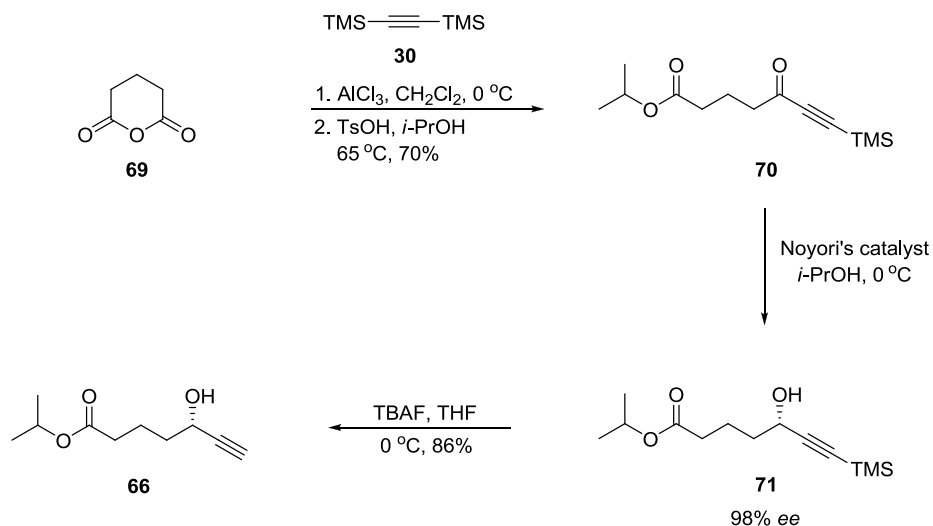
The final steps of the synthesis involved a Wittig olefination between the phosphonium salt **48** and the aldehyde **49** (Scheme 1.12). This gave the *Z*-alkene at the C₁₄–C₁₅ position. The product was then treated with TBAF to remove the TBDPS groups, affording the iodide **65** in 82% yield over 2 steps. A Suzuki reaction between the iodide **65** and the borane **47**, followed by silyl group deprotection, gave the target compound **22** in 55% yield in 2 steps.

The main advantage of this synthesis was the cheap starting materials used to prepare the key fragments **47** and **49**. The drawback however, was the number of steps required to synthesis the target compound. The longest linear sequence of resolvin E1 was 18 steps from 1,3-propanediol. This was 6 steps more than the synthesis reported by Petasis.¹⁸⁰ Thus, this pathway was not ideal for large scale production of resolvin E1.



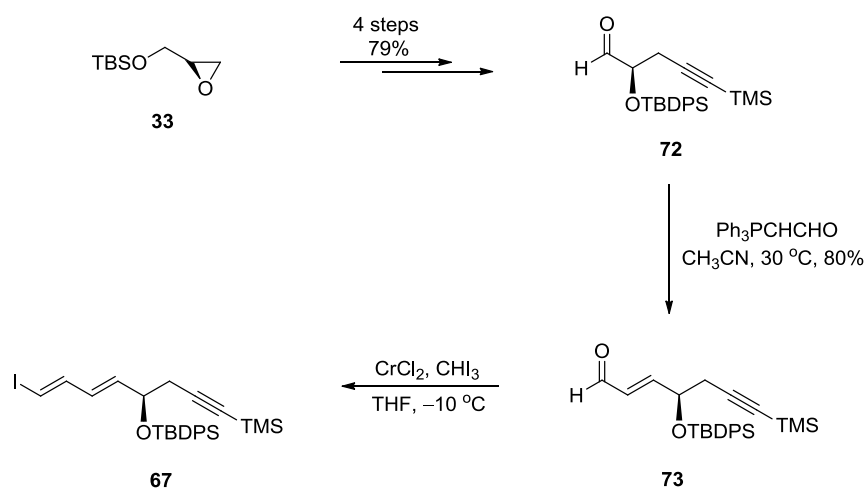
Scheme 1.13: Retrosynthesis of resolvin E1 developed by Allard.¹⁸²

Compound **66** was synthesised in 4 steps from glutaric anhydride **69** (Scheme 1.14). Treatment of **66** with compound **30** and aluminium chloride followed by the addition of *p*-toulenesulfonic acid and isopropyl alcohol gave the ketoester **70** in 70% yield over 2 steps. The ketone was asymmetrically reduced using Noyori's catalyst, giving the (*S*)-alcohol of compound **71** in 98% *ee*. Subsequent removal of the TMS group with TBAF furnished the ester **66** in 86% yield from compound **70**.



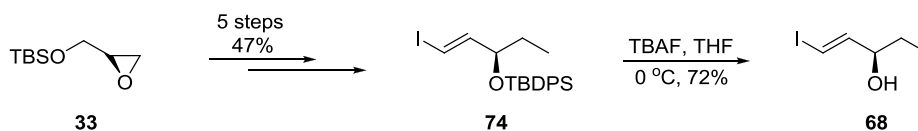
Scheme 1.14: Preparation of compound **66**.¹⁸²

Following the synthetic route described by Petasis¹⁸⁰ (Scheme 1.04), the aldehyde **72** was prepared in 4 steps from glycidol **33** (Scheme 1.15). This compound was then converted into the iodide **67** in 2 steps via a Wittig and Takai olefination.



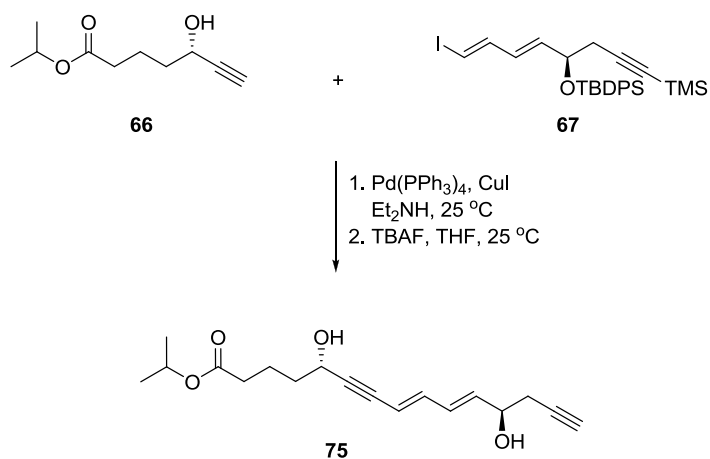
Scheme 1.15: Preparation of the iodide **67**.¹⁸²

The final intermediate **68** was synthesised using the pathway developed by Petasis (Scheme 1.05).¹⁸⁰ Starting from glycidol **33**, the iodide **74** was prepared in 47% yield in 5 steps (Scheme 1.16). The product was then treated with TBAF to afford compound **68** in 72% yield.



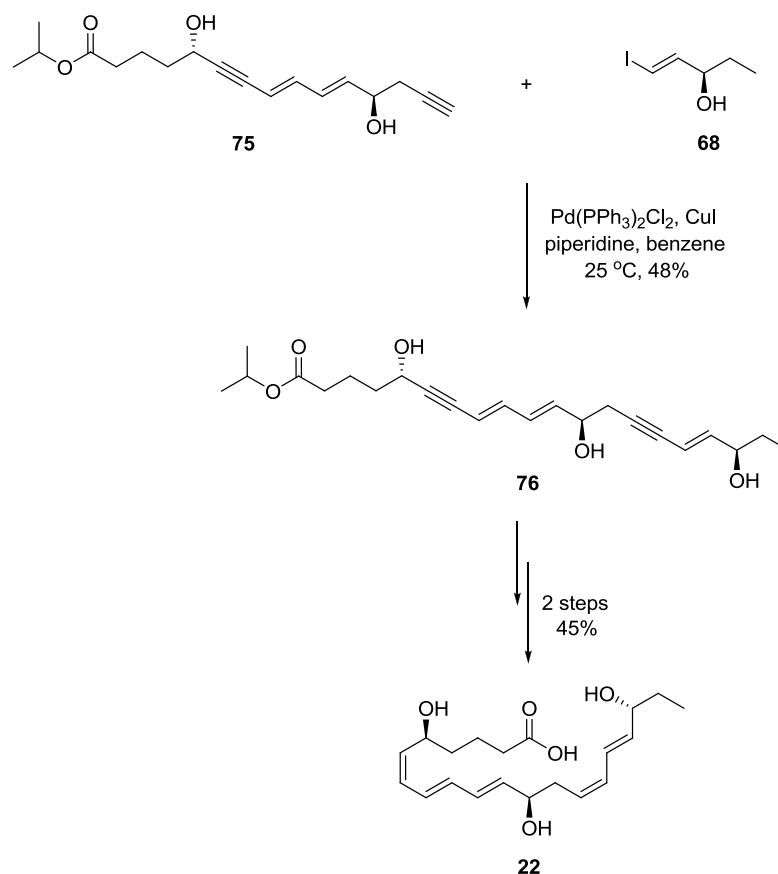
Scheme 1.16: Preparation of the iodide **68**.¹⁸²

Following the same strategy as Petasis,¹⁸⁰ the alkyne **66** and the iodide **67** were coupled together (Scheme 1.17). The product was treated with TBAF to remove the TMS and TBDPS groups, affording compound **75** as a single stereoisomer.



Scheme 1.17: Synthesis of compound **75**.¹⁸²

The antepenultimate step in the synthesis involved a second Sonogashira reaction between the alkyne **75** and the iodide **68** (Scheme 1.18). This furnished the product **76** as the isometrically pure 8*E*-alkene in 48% yield from compounds **66** and **67**. The two alkynes of compound **76** were reduced using a Zn(Cu/Ag) amalgam and the isopropyl ester was hydrolysed with NaOH to afford resolvins E1 **22** in 45% yield over 2 steps.



Scheme 1.18: Final steps in the synthesis of resolin E1.¹⁸²

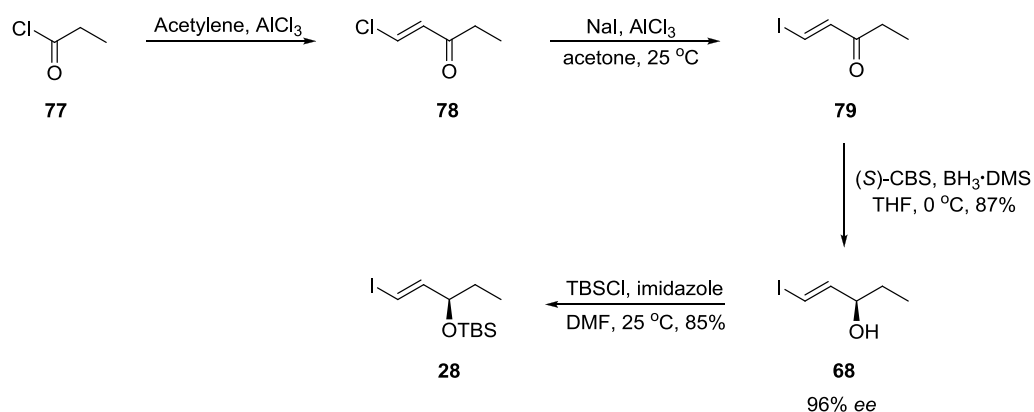
Following a similar pathway to Petasis,¹⁸⁰ Allard was able to optimise several reactions from this synthesis. One example was the asymmetric reduction of compound **70** using Noyori's catalyst. This gave the (*S*)-alcohol **71** in 98% *ee*. In contrast, Petasis reduced the ketone using *S*-Alpine-Borane[®] to give the (*S*)-enantiomer of alcohol **32** in only 90% *ee*.¹⁸⁰ By changing several reactions from the original synthesis,¹⁸⁰ the yield for the longest linear sequence of resolin E1 was 14% from glycidol **33**. This was higher than the yield reported by Petasis.¹⁸⁰

1.4.4 A scalable synthesis of compound **28**

An alternate synthesis that targeted the C₁₆–C₂₀ segment of resolin E1 was developed by Amin and co-workers in 2013 (Scheme 1.19).¹⁸⁵ The starting material for this pathway was the commercially available propionyl chloride **77**. This compound was cheaper than the starting material used by Petasis and Allard.¹⁸⁰⁻¹⁸² Subsequently, this synthetic route offered a viable alternative to afford the iodide **28**

on a multikilogram scale. This was important for the large scale production of resolvin E1 which was required for early-phase clinical testing.¹⁸⁵

Starting from propionyl chloride, the iodide **28** was synthesised in 16% yield in 4 steps (Scheme 1.19). The addition of acetylene to propionyl chloride afforded the chloride **78**. This compound was treated with sodium iodide and aluminium chloride to give compound **79**. The key step in the synthesis was the asymmetric reduction of the ketone. After testing a number of chiral reagents and reducing reagents, the (*S*)-(-)-2-methyl-CBS-oxazaborolidine catalyst and $\text{BH}_3\cdot\text{DMS}$ gave the (*R*)-alcohol in the highest enantiomeric purity. Using these reagents, the (*R*)-alcohol **68** was afforded in 87% yield and 96% *ee*. The alcohol **68** was then protected with a TBS group to afford the target compound **28** in 85% yield.



Scheme 1.19: Amin's scalable synthesis of the iodide **28**.¹⁸⁵

1.5 Resolvin E1 target receptors

1.5.1 ChemR23 and BLT-1

Resolvin E1 is able to regulate pro-inflammatory pathways by acting on the G protein-coupled receptors ChemR23 and BLT-1.^{171,186} Radio-ligand binding assays carried out by Arita et al. in 2005 showed resolvin E1 binds to a single site on the ChemR23 receptor with a high affinity ($K_i = 300 \text{ nM}$).¹⁷¹ Other receptors such as ALX, FPR and GPR1 that are known to regulate inflammation were screened. Resolvin E1 had no affinity for these receptors. Using dot blots containing mRNA from human tissues, Arita and co-workers showed that ChemR23 is expressed in a range of tissues including the testis, aorta, heart, brain, kidney, liver, lung, prostate

and gastrointestinal region.¹⁷¹ ChemR23 was also abundantly expressed in monocytes, macrophages and dendritic cells.¹⁷¹ Additional tests indicated that resolvin E1 inhibited pro-inflammatory TNF-induced NFκB activation in a concentration-dependent manner upon binding to ChemR23.¹⁷¹ This was supported by functional interaction studies that suggested resolvin E1 acts as a selective agonist for the ChemR23 receptor.¹⁷¹

Further studies by Arita and co-workers in 2007 also showed resolvin E1 binds to the leukotriene B₄ receptor BLT-1 with a high affinity ($K_i = 70$ nM).¹⁸⁶ Similar to the ChemR23 receptor, BLT-1 is expressed in neutrophils, monocytes and eosinophils.¹⁸⁷ Upon activation of the BLT-1 receptor by leukotriene B₄, these cells are recruited to the site of inflammation.¹⁸⁷ *In vitro* studies showed resolvin E1 mitigates this process by inhibiting the stimulation of leukotriene B₄ through calcium mobilisation. Resolvin E1 also attenuated leukotriene B₄ induced NFκB activation in BLT-1 transfected cells.¹⁸⁶ These results suggest that resolvin E1 dampens BLT-1 pro-inflammatory signals by acting as a leukotriene B₄ antagonist.

1.5.2 Chemerin

Despite the discovery that resolvin E1 acts on the ChemR23 and BLT-1 receptors, the exact binding site of this molecule is yet to be established. Chemerin, the natural agonist of the ChemR23 receptor, could hold the key to solving this problem. Chemerin belongs to the polypeptide family of cathelicidin and cystatin proteins which eradicate microbes and pathogens.¹⁸⁸⁻¹⁹⁰ Chemerin is known to exhibit anti-inflammatory properties similar to resolvin E1, promoting chemotaxis and calcium release in immature macrophages and dendritic cells.¹⁹¹⁻¹⁹²

Through a series of structure-function relationship studies conducted in 2004, Wittamer and co-workers identified a nine amino acid sequence derived from the chemerin C-terminus responsible for ChemR23 agonism.¹⁹³ The chemerin-9 nonapeptide (Tyr¹⁴⁹-Phe¹⁵⁰-Pro¹⁵¹-Gly¹⁵²-Gln¹⁵³-Phe¹⁵⁴-Ala¹⁵⁵-Phe¹⁵⁶-Ser¹⁵⁷) was shown to have a similar binding affinity and biological activity as the full sized chemerin protein.¹⁹³

Several nonapeptide analogues were synthesised by Wittamer and co-workers to determine the key amino acids that activate the ChemR23 receptor. Compared to the unsubstituted nonapeptide ($EC_{50} = 7.1$ nM), moderate decreases in the bioactivity of these analogues were observed when Pro¹⁵¹, Gln¹⁵³ and Ser¹⁵⁷ were exchanged with alanine ($EC_{50} = 42.5$ nM, 35.8 nM and 48.3 nM respectively). However, when the Tyr¹⁴⁹, Phe¹⁵⁰ and Gly¹⁵² residues were altered, the peptide potency was dramatically reduced by more than two orders of magnitude ($EC_{50} = 496$ nM, 155 nM and 6.7 μ M respectively).¹⁹³ On the basis of unpublished studies¹⁹⁴ and molecular modelling, the image in Figure 1.12 represents a plausible binding mode of chemerin-9. The four amino acids Tyr¹⁴⁹-Phe¹⁵⁰-Pro¹⁵¹-Gly¹⁵² at the *N*-terminus of the nonapeptide form a loop at the active site of the receptor. Substituting these amino acids with alanine would change the size of the loop, thus reducing the binding affinity and the potency of the peptide. This is consistent with the findings made by Wittamer.¹⁹³

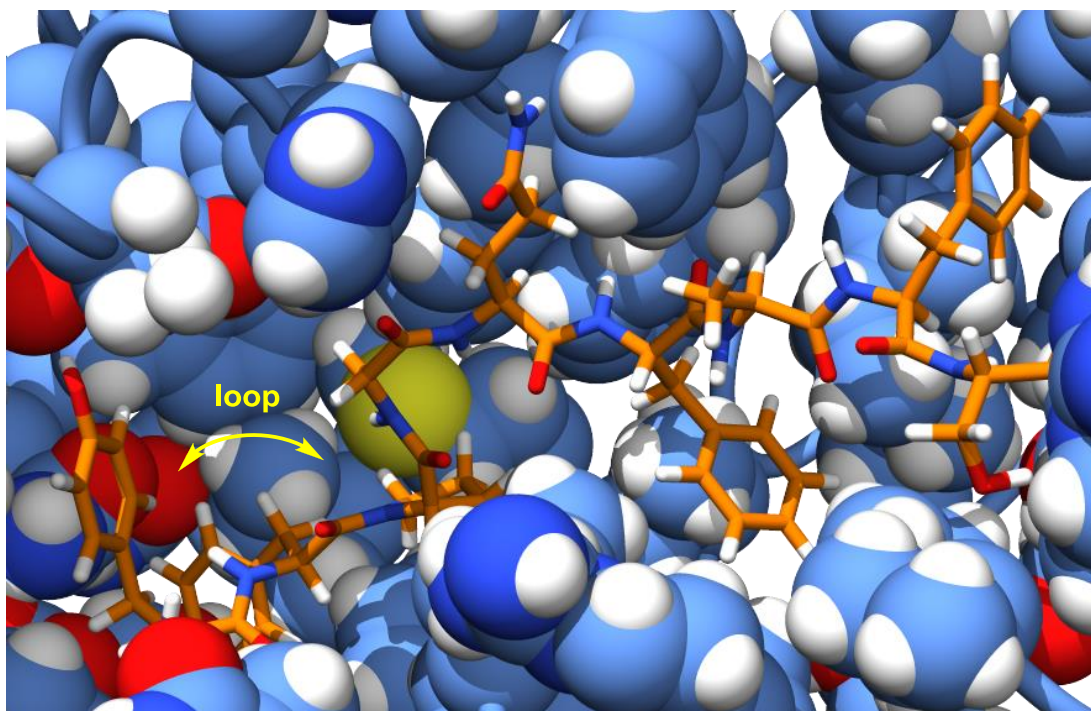


Figure 1.12: Chemerin-9 bound to the ChemR23 receptor.

Although the exact site on the ChemR23 receptor to which resolvin E1 binds is yet to be determined, it has been postulated that it could bind to the same site as the chemerin-9 peptide.^{1,194} This is based on the structural similarities between the two molecules. A comparison of the 3D molecular models of resolvin E1 and chemerin-9

is shown in Figure 1.13. When bound to ChemR23, the chemerin-9 peptide adopts a loop-like geometry. This allows the peptide to bind tightly to the receptor. Resolvin E1 also has a loop that is formed by the 6Z-alkene (Figure 1.13). This provides the molecule with a conformational rigidity similar to chemerin-9. Resolvin E1 modelled into the ChemR23 receptor showed this loop fits in the same pocket as the loop of chemerin-9. Thus, it is speculated that the two compounds could bind to the ChemR23 receptor at the same site.

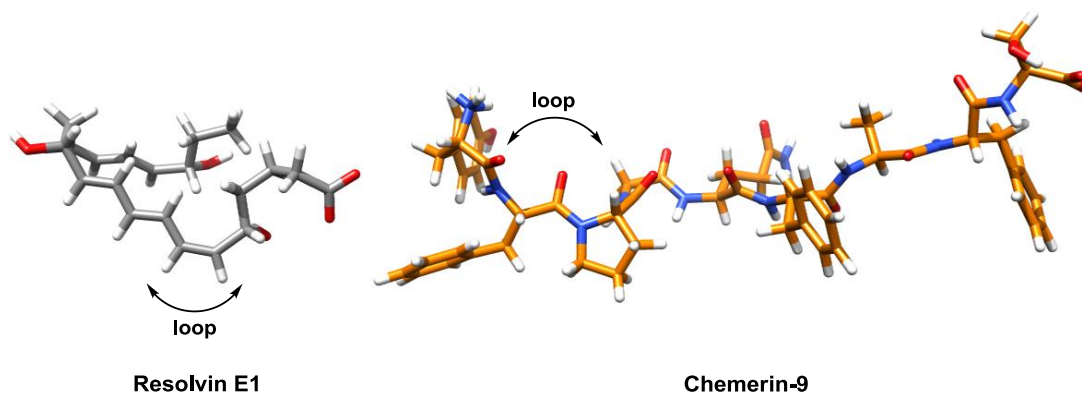


Figure 1.13: 3D molecular structures of resolvin E1 and chemerin-9.

1.6 Chemical stability of resolvin E1

Although resolvin E1 is a potent pro-resolving lipid mediator, it is also highly unstable. This was confirmed by *in vitro* stability studies conducted by Maddipati and Zhou in 2011.¹⁹⁵ The studies showed that when incubated with a phosphate buffered solution at 0 °C, 25 °C, and 37 °C, the concentration of resolvin E1 reduced significantly over 48 hours, as judged by HPLC-MS. It was estimated that the half-life of resolvin E1 at 25 °C in this buffered system was 18 hours (Figure 1.14). Rapid degradation of resolvin E1 was also observed when incubated with a complex mineral medium such as Roswell Park Memorial Medium 1640.¹⁹⁵

The decomposition of resolvin E1 could be attributed to the chemical instability of the triene system which is highlighted in red (Figure 1.14).¹⁸¹ The *Z*-alkene at the C₆–C₇ position can readily isomerise to the more thermodynamically stable *E*-alkene, giving compound **80**.¹⁷² This isomer has a significantly reduced anti-inflammatory activity.¹⁷⁷ Biological tests conducted by Serhan and co-workers have shown this isomer to be 70% less potent than resolvin E1 at reducing leukocyte

infiltration.¹⁷⁶⁻¹⁷⁸ This decrease in anti-inflammatory activity could be attributed to a change in the conformation of the two isomers. Upon isomerisation, resolvins E1 adopts a linear structure rather than a loop-like geometry (Figure 1.14). The loss of chemical rigidity prevents compound **80** from binding tightly to the ChemR23 receptor as it can no longer fit in the proposed pocket. Subsequently, the anti-inflammatory potency of the 6*E*-isomer is diminished.

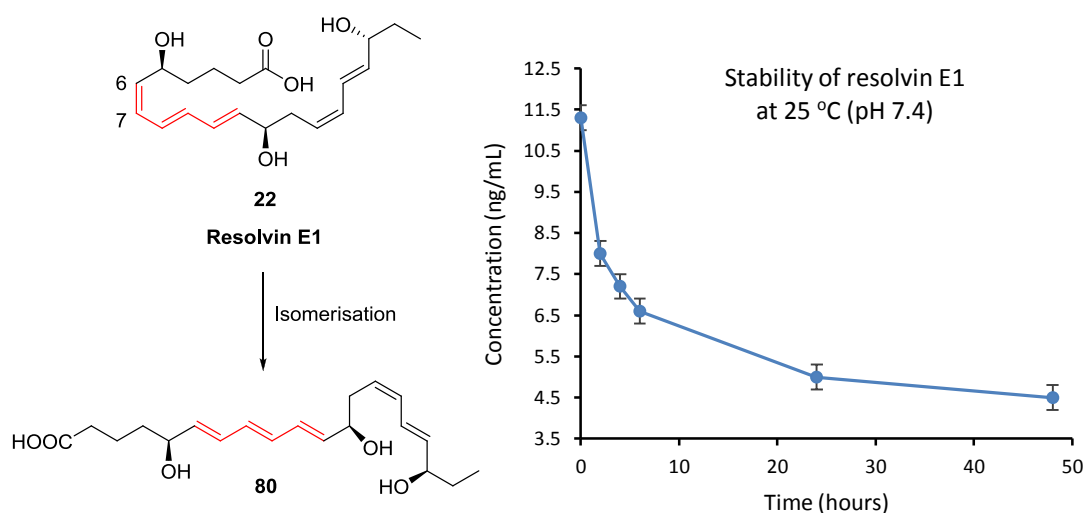
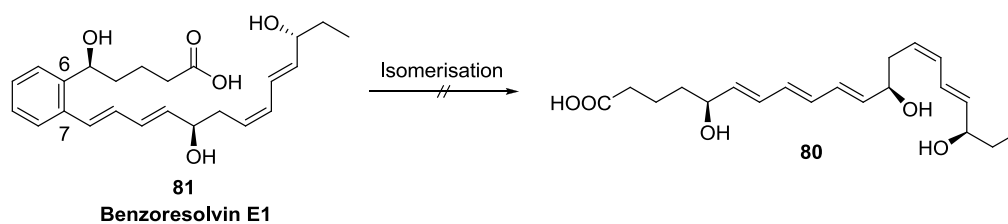


Figure 1.14: Resolvin E1 stability plot and isomerisation of the triene unit.¹⁹⁵

1.7 Project aims

The aims of this project were to synthesise an analogue of resolvins E1, investigate its chemical stability and determine its affinity for the BLT-1 receptor using a radio-ligand binding assay. The target compound chosen for this study was a benzene annulated analogue of resolvins E1, herein referred to as benzo-resolvins E1 **81** (Scheme 1.20). As previously mentioned,^{172,181} the 6*Z*-alkene of resolvins E1 readily isomerises at room temperature to the more thermodynamically stable 6*E*-alkene. This results in a loss of anti-inflammatory potency.¹⁷⁷ By adding a benzene ring, isomerisation could no longer take place at this position (Scheme 1.20). With this decomposition pathway suppressed, it is envisaged that benzo-resolvins E1 would be more stable and have a longer lasting anti-inflammatory action than resolvins E1.



Scheme 1.20: The benzene ring of compound **81** inhibits isomerisation at the C₆–C₇ position.

Based on molecular modelling studies with resolvins E1 and the ChemR23 receptor,¹⁹⁴ the benzene ring could also utilise an extra hydrophobic pocket at the proposed binding site (Figure 1.15). The benzene ring would be in proximity to the phenyl alanine residue of the ChemR23 receptor and could undergo π - π stacking. Subsequently, the benzene annulated analogue of resolvins E1 should have a greater affinity for the ChemR23 receptor, thus prolonging its anti-inflammatory action.

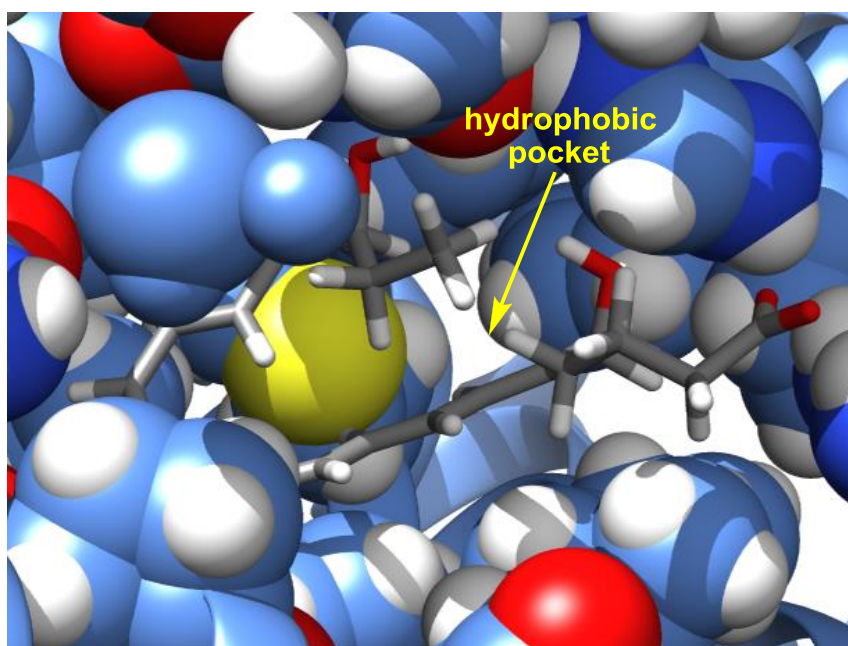
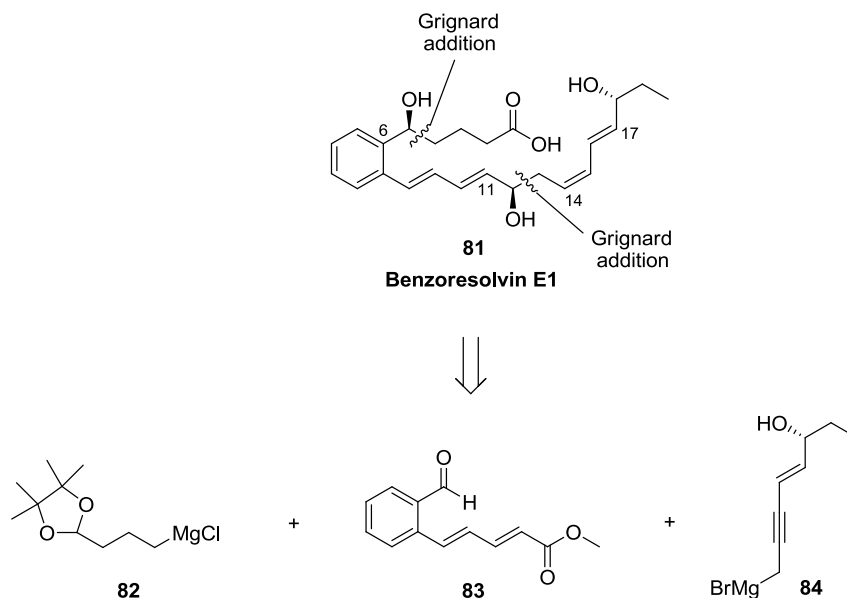


Figure 1.15: Proposed binding site for resolvins E1.

1.7.1 Synthesis of benzoeresolvin E1

The target compound **81** could be synthesised from the intermediates **82**, **83** and **84**, with the key disconnections located at the C₄–C₅ and the C₁₂–C₁₃ positions (Scheme 1.21). Unlike the pathways developed by Petasis, Kobayashi and Allard,¹⁸⁰⁻¹⁸² cross-coupling reactions were not used in the proposed synthetic route. Instead, a Grignard

strategy was planned for benzoeresolvin E1. This offered an alternate pathway to prepare the C₆–C₁₁ benzodiene and the C₁₄–C₁₇ diene of the target compound. The planned synthesis involved a fewer number of steps to the pathways described in the literature.¹⁸⁰⁻¹⁸²



Scheme 1.21: Proposed retrosynthesis of benzoeresolvin E1 **81**.

1.7.2 Stability study

Once benzoeresolvin E1 is synthesised, the stability of this compound in a phosphate buffered solution will be investigated and compared to resolvin E1. This study will determine the importance of the benzene ring towards improving the stability of this messenger molecule by blocking isomerisation at the C₆–C₇ position.

1.7.3 Inhibition of BLT-1 and preparation of analogues

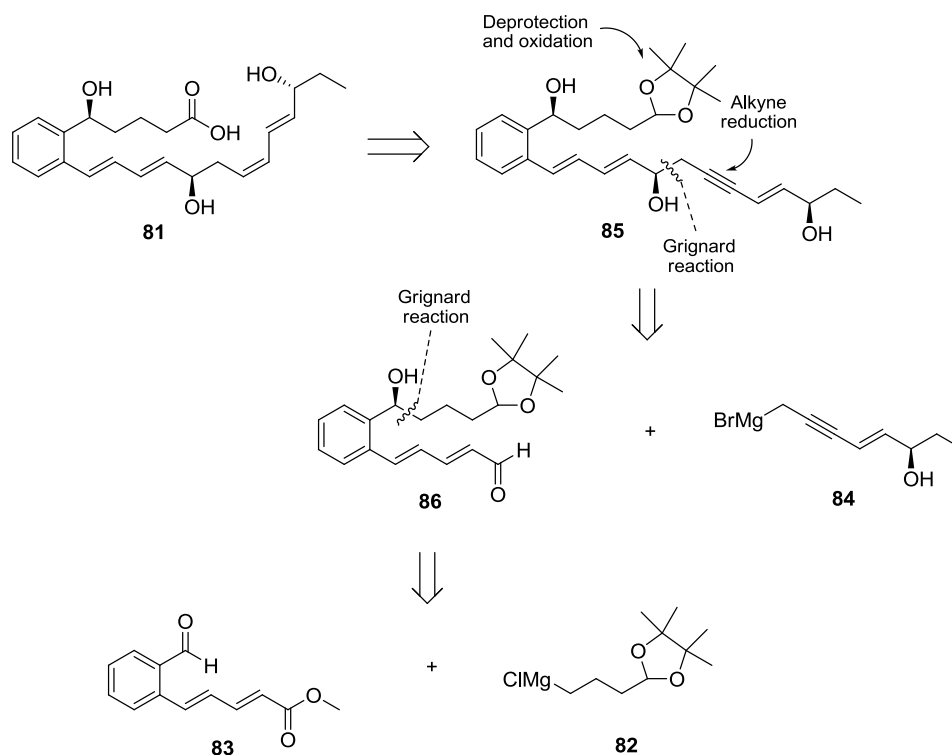
To determine the affinity of benzoeresolvin E1 **81** for the BLT-1 receptor, radio-ligand assays will be conducted by Eurofins Panlabs in Taiwan. BLT-1 will be used instead of ChemR23 since it is available for testing. The target compound will be initially screened with the BLT-1 receptor at 10⁻⁵ M. This will be followed by a semi-quantitative analysis to determine the IC₅₀ and inhibitory constant of **81**. If these results are positive, analogues of benzoeresolvin E1 will be synthesised to improve the anti-inflammatory action of the target compound.

Chapter 2

Synthesis of Benzoeresolvin E1: A Grignard Strategy

2.1 Proposed synthetic pathway

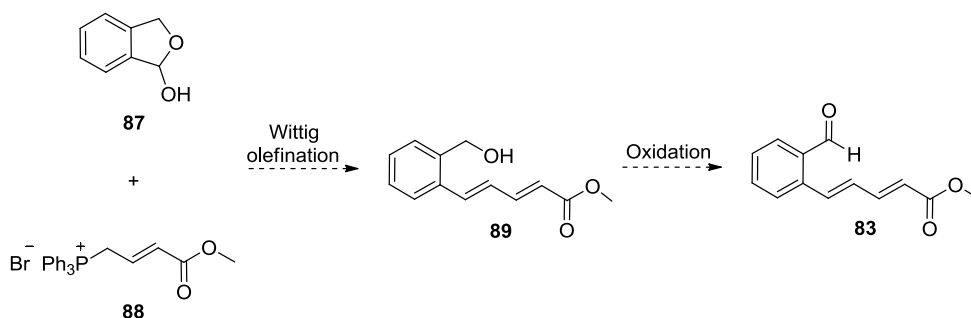
Benzoeresolvin E1 **81** could be synthesised from the pathway shown in Scheme 2.01. The target compound could be prepared from the triol **85** in 3 steps. These steps include the reduction of the alkyne, removal of the acetal group and oxidation of the aldehyde to give the carboxylic acid of benzoeresolvin E1 **81**. Compound **85** could be prepared by an addition reaction between the aldehyde **86** and the propargylic Grignard **84**. Examples of propargylic Grignards similar to **84** are known, although they are limited in the literature.^{196,197} Finally, the aldehyde **83** could be prepared by a second Grignard reaction between the aldehyde **83** and the Grignard reagent **82** followed by reduction of the methyl ester.



Scheme 2.01: Proposed retrosynthesis of benzoeresolvin E1 **81**.

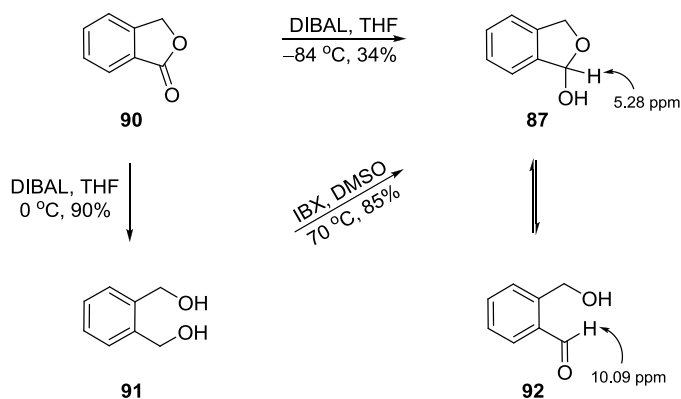
2.2 Preparation of fragment 83

Focusing on the synthesis of the aldehyde **83**, this compound could be prepared in 2 steps. A Wittig olefination between the lactol **87** and the phosphonium salt **88** could give the alcohol **89**. The benzyl alcohol could then be oxidised to afford the aldehyde **83** (Scheme 2.02).



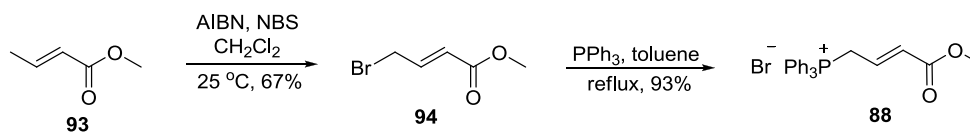
Scheme 2.02: Proposed synthesis of the aldehyde **83**.

The lactol **87** was synthesised in 34% yield along with the diol **91** in 40% yield by the reduction of phthalide **90** with DIBAL at -84°C (Scheme 2.03).¹⁹⁸ Under normal laboratory conditions, the lactol **87** is in equilibrium with the aldehyde **92**.¹⁹⁹ The ^1H NMR spectrum of the product showed a 34:16 mixture of the lactol **87** and the aldehyde **92**, with the signal at 10.09 ppm ascribed to the aldehyde hydrogen of **92** and the resonance at 5.28 ppm attributed to the methine hydrogen of the lactol **87**. These signals are consistent with the resonances observed in the ^1H NMR spectrum provided in the literature.¹⁹⁹ Alternatively, phthalide **90** was completely reduced to the diol **91** in 90% yield. Following the method described by Corey and Palani,¹⁹⁹ the diol **91** was then selectively oxidised using IBX to give the lactol **87** in 77% yield over 2 steps (Scheme 2.03).



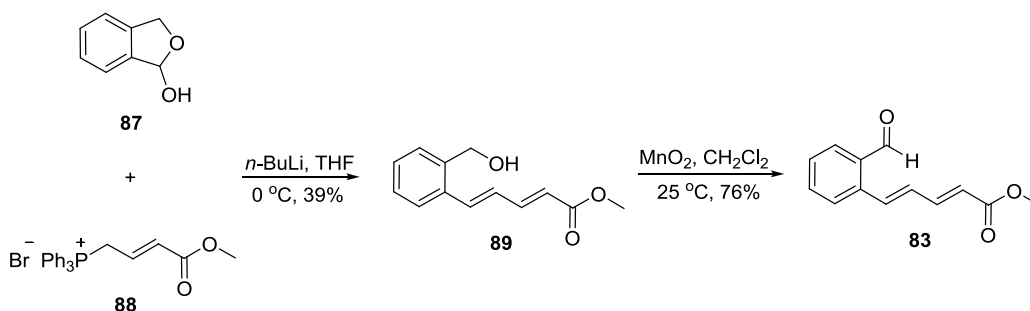
Scheme 2.03: Preparation of the lactol **87**.

Compound **88** was synthesised following the procedure described by Baeckstroem and co-workers.²⁰⁰ Radical bromination of methyl crotonate **93** using AIBN and *N*-bromosuccinimide gave the bromide **94** in 67% yield. This compound was then treated with triphenylphosphine to afford the phosphonium salt **88** in 93% yield (Scheme 2.04).



Scheme 2.04: Preparation of compound **88**.

Addition of *n*-BuLi to compound **88** in anhydrous tetrahydrofuran followed by the addition of the lactol **87** at 0 °C furnished the alcohol **89** in 39% yield (Scheme 2.05). The ¹H NMR spectrum of the crude reaction mixture showed the reaction proceeded with complete selectivity for the *4E*-alkene. The product was then dissolved in dichloromethane and treated with activated manganese dioxide to afford the aldehyde **83** in 76% yield (Scheme 2.05).



Scheme 2.05: Synthesis of the aldehyde **83**.

The ^1H NMR spectrum of the product showed four signals at 7.85, 7.49, 6.81 and 6.02 ppm that were attributed to the four vinylic hydrogens while the signals at 7.80, 7.64, 7.56 and 7.46 ppm were ascribed to the four aromatic hydrogens (Figure 2.01). The vinylic signals at 6.81 and 7.85 ppm have a common coupling constant of 15.5 Hz while the vinylic resonances at 6.02 and 7.49 ppm have a coupling constant of 15.4 Hz. This supports the *2E,4E*-diene arrangement of **83**. A signal at 10.21 ppm that was ascribed to the hydrogen of the aldehyde was also observed in the ^1H NMR spectrum.

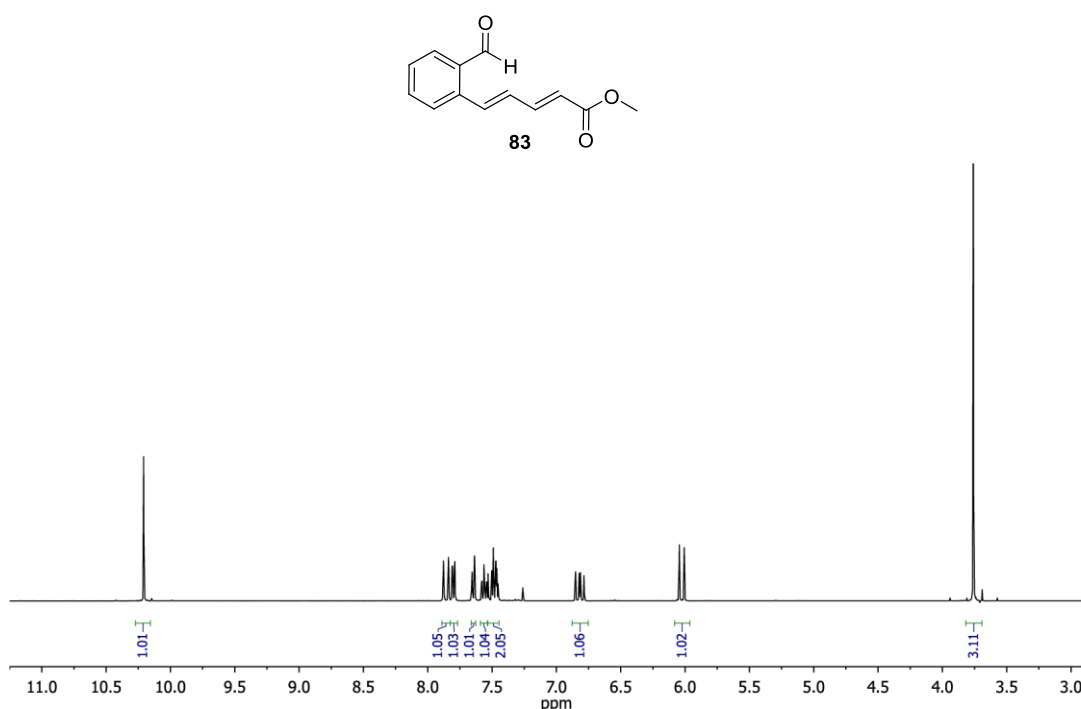


Figure 2.01: ^1H NMR spectrum of the aldehyde **83** in CDCl_3 .

2.3 Investigating the selectivity of the Grignard reaction

With aldehyde **83** in hand, attention was focused on the reaction between this compound and the Grignard reagent **82**. It was anticipated that **82** would add to the aldehyde to give the alcohol **86** after the methyl ester was reduced (Scheme 2.01). However, the Grignard reagent could also add to the ester via a 1,2-addition or a Michael addition (Figure 2.02). To determine the selectivity of the Grignard reaction, the model reaction between ethylmagnesium bromide and compound **83** was investigated.

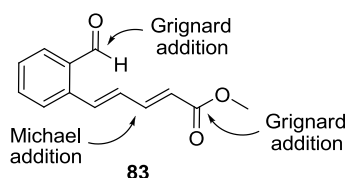
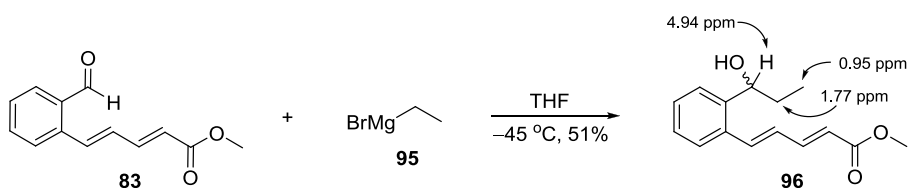


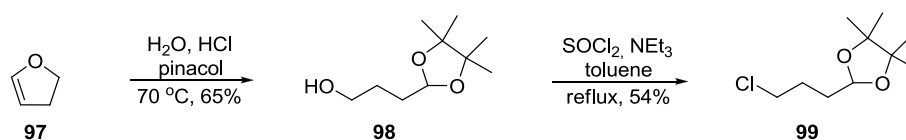
Figure 2.02: Possible sites for the addition of a Grignard reagent.

Pleasingly, the addition of one equivalent of ethylmagnesium bromide to the aldehyde **83** in anhydrous tetrahydrofuran at $-45\text{ }^{\circ}\text{C}$ afforded compound **96** as the sole product in 51% yield (Scheme 2.06). The methyl ester remained intact, as suggested by the signal at 167.6 ppm in the ^{13}C NMR spectrum and the peak at 1709 cm^{-1} in the IR spectrum of the crude reaction mixture. The ^1H NMR spectrum of the product showed a triplet at 4.94 ppm that was ascribed to the methine hydrogen of the carbon bearing hydroxyl group while the appearance of two signals at 1.77 and 0.95 ppm were assigned to the methylene and methyl hydrogens of the newly formed ethyl group.



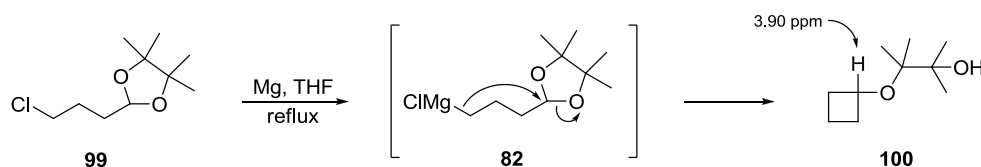
Scheme 2.06: Addition of ethylmagnesium bromide to the aldehyde **83**.

Having selectively reacted ethylmagnesium bromide with compound **83**, attention was shifted towards the preparation of the Grignard **82**. The key feature of this Grignard reagent is the acetal group, which is used as a masked carboxylic acid in the synthesis of benzo-resolvin E1. The Grignard reagent **82** was synthesised in 3 steps starting from 2,3-dihydrofuran. Following the procedure by Stowell and Polito,²⁰¹ 2,3-dihydrofuran was treated with a catalytic amount of concentrated HCl (32% w/v) and pinacol in water to furnish the alcohol **98** in 65% yield (Scheme 2.07). The alcohol was then converted into a chloro group using thionyl chloride and triethylamine to afford compound **99** in 54% yield.



Scheme 2.07: Preparation of compound **99**.

In an attempt to synthesise the Grignard reagent **82**, a 1 M solution of **99** in tetrahydrofuran was heated under reflux with magnesium turnings. After 4 hours, a complex mixture of signals was observed in the region of 0.50–4.00 ppm in the ^1H NMR spectrum of the crude reaction mixture. These signals could be assigned to a combination of polymerised and thermally induced decomposition products, with cyclobutyl ether **100** identified as the major compound (Scheme 2.08). The ^1H NMR spectrum of the crude reaction mixture showed a multiplet at 3.90 ppm that could be attributed to the methine hydrogen of **100** along with a cluster of signals between 1.20–3.50 ppm that could be assigned to the methylene and methyl hydrogens. It was rationalised that the Grignard reagent **82** underwent a thermally induced intramolecular nucleophilic substitution reaction to afford the cyclobutyl ether **100** (Scheme 2.08). This was consistent with the decomposition product reported by Forbes and co-workers.²⁰²

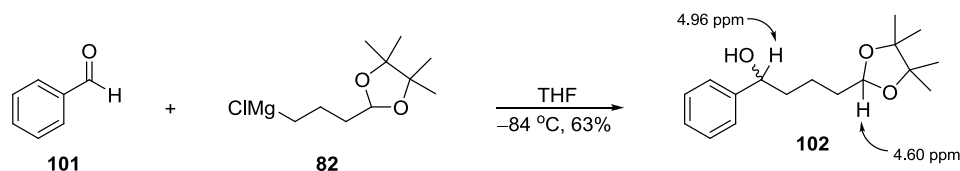


Scheme 2.08: Thermally induced decomposition of the Grignard reagent **82**.

To prevent this competing reaction, the Grignard reaction was repeated at 0 °C. Pleasingly, the cyclobutyl ether **100** was not observed in the ^1H NMR spectrum of the crude mixture after this change. Titrating the Grignard reagent **82** with BHT and 1,10-phenanthroline in anhydrous tetrahydrofuran suggested that the yield of this reaction was 79% after 19 hours.

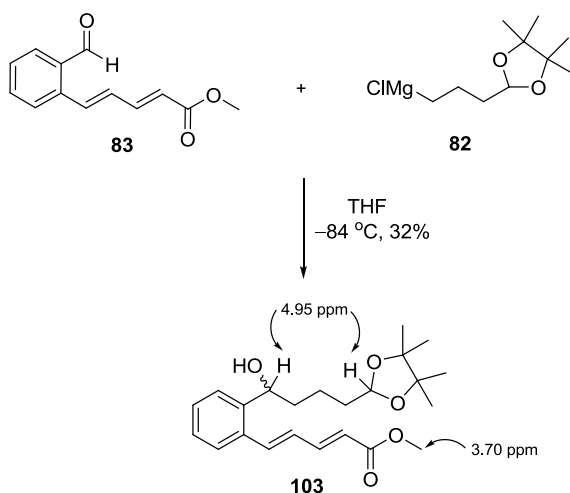
Benzaldehyde was then used as a model compound to investigate the reactivity of the Grignard reagent **82**. Addition of one equivalent of this Grignard to benzaldehyde at –84 °C furnished the alcohol **102** in 63% yield (Scheme 2.09). The ^1H NMR spectrum of the product showed the appearance of a triplet at 4.96 ppm that

was ascribed to the methine hydrogen of the newly formed benzylic alcohol. A doublet of doublets at 4.60 ppm was also observed in the spectrum. This could be assigned to the methine hydrogen of the acetal group. The IR spectrum of the product also showed a new peak at 3446 cm^{-1} that could be ascribed to the newly formed benzylic alcohol.



Scheme 2.09: Addition of the Grignard reagent **82** to benzaldehyde.

Following the same conditions described in the model system, the aldehyde **83** was treated with one equivalent of the Grignard reagent **82** at $-84\text{ }^{\circ}\text{C}$ to afford the alcohol **103** in 32% yield after 5 hours (Scheme 2.10). Starting material was also recovered in 68% yield from the reaction mixture.



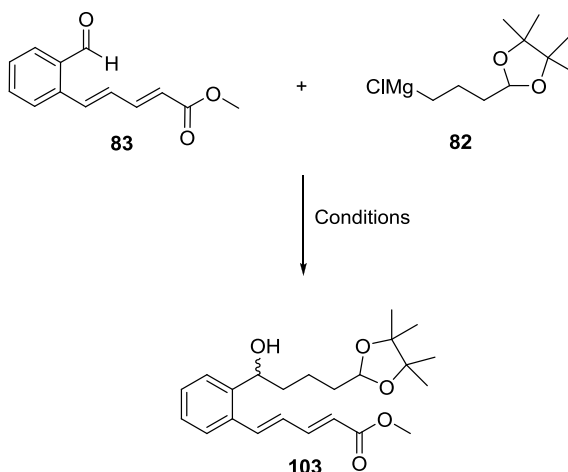
Scheme 2.10: Addition of the Grignard reagent **82** to compound **83**.

The ^1H NMR spectrum of the product showed eight signals between 5.92–7.42 ppm that were ascribed to the four vinylic and four aromatic hydrogens. The two methine hydrogens of the acetal and the carbon bearing hydroxyl group were assigned to the two superimposed signals at 4.95 ppm while the singlet at 3.70 ppm was ascribed to the methyl hydrogens of the ester. The ^{13}C NMR spectrum showed a signal at 167.6 ppm that was assigned to the carbonyl carbon. Furthermore, a molecular ion

was observed at $m/z = 388.2234$ [M^+] in the high resolution mass spectrum. This was consistent with the molecular formula required for $C_{23}H_{32}O_5$.

Similar yields of compound **103** were afforded when the reaction mixture was warmed to $-45\text{ }^{\circ}\text{C}$ and $0\text{ }^{\circ}\text{C}$ (Table 2.01, entries 2 and 3). Repeating the reaction with 1.5 equivalents of the Grignard reagent **82** gave a complex mixture of products (Table 2.01, entry 4). The use of $\text{LnCl}_3 \cdot \text{LiCl}$ to promote the addition reaction of **82** to the aldehyde was also explored.²⁰³ One equivalent of the Grignard **82** was added dropwise to a mixture of one equivalent of $\text{LnCl}_3 \cdot \text{LiCl}$ and compound **83** in anhydrous tetrahydrofuran. This furnished the alcohol **103** in 29% yield and starting material in 65% yield after 12 hours at $0\text{ }^{\circ}\text{C}$ (Table 2.01, entry 5). Changing the solvent to diethyl ether also afforded the alcohol **103**, however in a lower yield of 12% (Table 2.01, entry 6).

Table 2.01: Conditions tested for the addition of the Grignard **82** to compound **83**.



Entry	82 (eq.)	Conditions	Result
1	1.0	THF, $-84\text{ }^{\circ}\text{C}$, 5 hrs	103 (32%)
2	1.0	THF, $-45\text{ }^{\circ}\text{C}$, 5 hrs	103 (32%)
3	1.0	THF, $0\text{ }^{\circ}\text{C}$, 5 hrs	103 (31%)
4	1.5	THF, $0\text{ }^{\circ}\text{C}$, 5 hrs	complex mixture
5	1.0	$\text{LnCl}_3 \cdot \text{LiCl}$ (1 eq.), THF, $0\text{ }^{\circ}\text{C}$, 12 hrs	103 (29%)
6	1.0	$\text{LnCl}_3 \cdot \text{LiCl}$ (1 eq.), Et_2O , $0\text{ }^{\circ}\text{C}$, 12 hrs	103 (12%)

2.4 Preparation of the C₁₃–C₂₀ terminal chain

In light of the low yields of compound **103**, the addition of the Grignard reagent **82** was postponed to a later stage in the synthesis. Instead, focus was shifted towards the synthesis of the Grignard reagent **84**. This compound would provide the 14*Z*,16*E*-diene fragment of benzoiresolvin E1 (Figure 2.03).

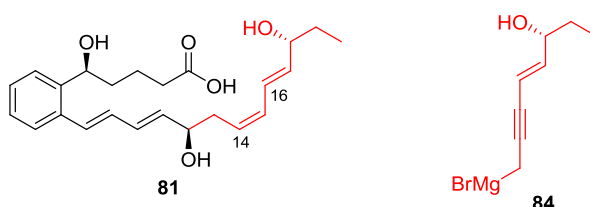
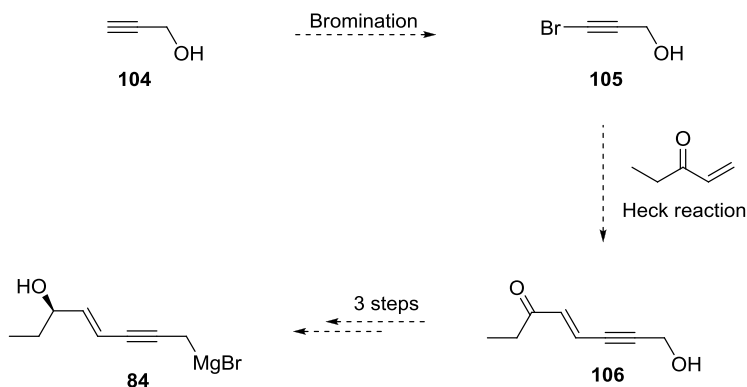


Figure 2.03: Benzoiresolvin E1 and the Grignard reagent **84**.

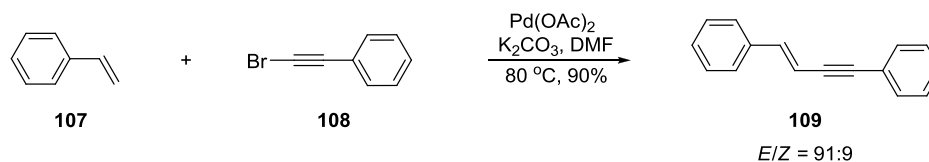
The Grignard reagent **84** is a key intermediate in the synthesis of benzoiresolvin E1 and could be prepared from propargyl alcohol in 5 steps (Scheme 2.11). Propargyl alcohol could be brominated to afford the bromide **105**. A Heck reaction with this compound and ethyl vinyl ketone could give the enyne portion of compound **106**. The target compound **84** could then be synthesised from **106** in 3 steps by an Appel reaction, reduction of the ketone and preparation of the Grignard.



Scheme 2.11: Proposed pathway for the synthesis of the Grignard reagent **84**.

Starting from propargyl alcohol, the bromide **105** was synthesised in 91% yield using silver nitrate and *N*-bromosuccinimide in acetone.²⁰⁴ This method proved superior to the bromination outlined by Brandsma which utilised potassium hypobromite as the oxidant.²⁰⁵ The enyne **106** could be prepared from the bromide **105** by adapting the Heck reaction conditions reported by Wen and Jeffery

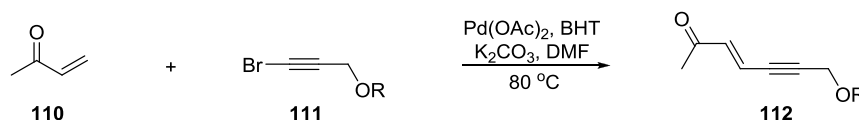
(Scheme 2.12).²⁰⁶⁻²⁰⁷ By coupling bromophenylacetylene **108** with a range of unactivated alkenes, Wen and co-workers prepared conjugated enynes such as **109** in high yields.²⁰⁶ These reactions were selective towards the *E*-alkene.



Scheme 2.12: Heck coupling between styrene **107** and the bromide **108** reported by Wen.²⁰⁶

Using the same conditions reported by Wen,²⁰⁶ the bromide **105** was treated with 20 equivalents of methyl vinyl ketone, palladium acetate (5 mol%), 2.5 equivalents of potassium carbonate and a catalytic amount of BHT in dimethylformamide (Table 2.02, entry 1). Methyl vinyl ketone was used as a model compound for ethyl vinyl ketone as it is cheaper while BHT was used as a radical scavenger to prevent polymerisation of the starting material and the product. The reaction turned black after stirring the mixture for 2 hours at 80 °C (Table 2.02, entry 1). The ¹H NMR spectrum of the crude reaction mixture showed signals between 0.50–2.00 ppm with no resonances observed in the vinylic region, suggesting decomposition of the reaction mixture. Protecting the alcohol with a TBS group also gave the same result (Table 2.02, entry 2). The bromide **105** was then protected with a tetrahydropyranyl group (THP) and the reaction was repeated using the same conditions (Table 2.02, entry 3). This gave the enyne **112** in 16% yield after 2 hours along with an unidentified mixture of compounds.

Table 2.02: Heck coupling reaction with the protected alcohol **111** and methyl vinyl ketone.



Entry	R	Reaction time	Product yield
1	H	2 hrs	decomposition
2	TBS	2 hrs	decomposition
3	THP	2 hrs	16%

Structural elucidation of the product **112** was based on the ¹H NMR and ¹³C NMR spectra. The ¹H NMR spectrum showed two signals at 6.59 and 6.46 ppm that could

be assigned to the newly formed vinylic hydrogens (Figure 2.04). These hydrogens have a common coupling constant of 16.2 Hz which is consistent with the *E*-alkene of **112**. The triplet at 4.78 ppm was ascribed to the methine hydrogen of the THP group while the two signals at 4.44 and 4.37 ppm could be assigned to the propargylic hydrogens. The ^{13}C NMR spectrum showed a signal at 197.0 ppm that was ascribed to the ketone while the two resonances at 138.5 and 123.3 ppm were assigned to the vinylic carbons. Two signals at 97.2 and 96.0 ppm were also observed in the spectrum. These were attributed to the two acetylenic carbons.

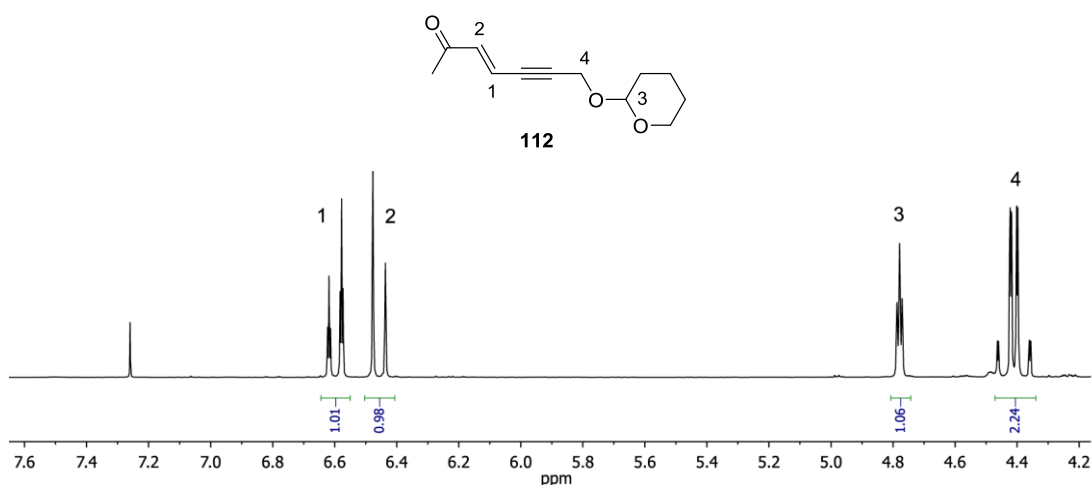
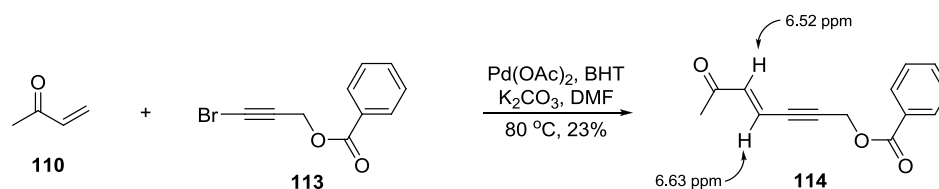


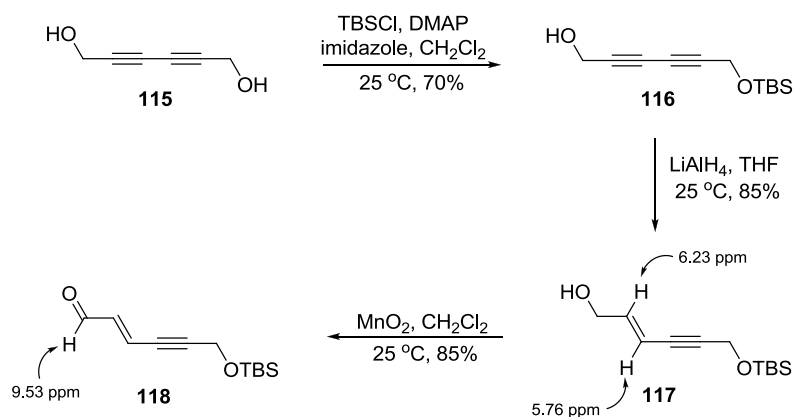
Figure 2.04: ^1H NMR spectrum of compound **112** in CDCl_3 (4.20–7.60 ppm).

The low yields of **112** could be due to the hydrolysis of the THP group caused by the mild Lewis acidity of the $\text{Pd}(\text{OAc})_2$. Subsequently, propargyl alcohol was treated with benzoyl chloride to form the benzoate ester **113** (Scheme 2.13). It was anticipated that the ester would be more stable than the THP protecting group. Following the same conditions given in Table 2.02, compound **114** was afforded in 23% yield after 2 hours (Scheme 2.13). The key signals in the ^1H NMR spectrum of the product were observed at 6.63 and 6.52 ppm. These were ascribed to the two vinylic hydrogens. In an attempt to improve the yield of the product, the reaction was repeated and the mixture was stirred for 4 hours. Only trace amounts of the product was observed in the ^1H NMR spectrum after this time, indicating that decomposition had occurred. This suggests that the α,β -unsaturated enyne system is unstable under these conditions.



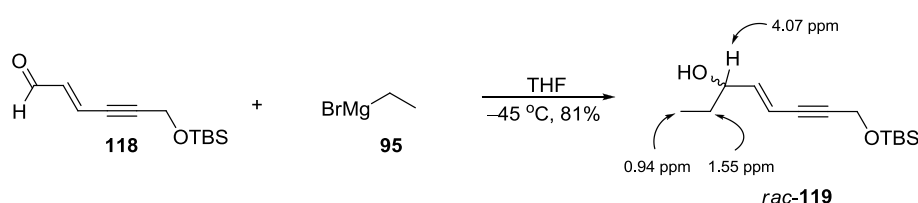
Scheme 2.13: Heck reaction between methyl vinyl ketone and the bromide **113**.

In light of the low yields for the Heck products, an alternate pathway towards the Grignard reagent **84** was explored (Scheme 2.14). 2,4-Hexadiyne-1,6-diol **115** was the starting material for this synthesis. This compound was prepared on a large scale in 25% yield using propargyl alcohol, CuCl and O_2 .²⁰⁵ Following the pathway reported by Trost and Livingston,²⁰⁸ the aldehyde **118** was synthesised from 2,4-hexadiyne-1,6-diol **115** in 3 steps (Scheme 2.14). Monosilylation of the diol **115** using TBSCl, imidazole and DMAP furnished compound **116** in 70% yield. The propargylic alkyne was reduced to an alkene using LiAlH_4 to afford compound **117** in 85% yield. The appearance of two new resonances at 6.23 and 5.76 ppm in the ^1H NMR spectrum of the product were ascribed to the newly formed vinylic hydrogens. These signals have a common coupling constant of 15.9 Hz. This is consistent with the coupling constant expected for an *E*-alkene. The allylic alcohol was then oxidised to an aldehyde to give compound **118** in 85% yield. The ^1H NMR spectrum of the product showed a doublet at 9.53 ppm that was attributed to the aldehyde hydrogen. Unlike the Heck reaction in Scheme 2.13, this synthetic route allowed access to the enyne under milder conditions and gave higher yields of the product.



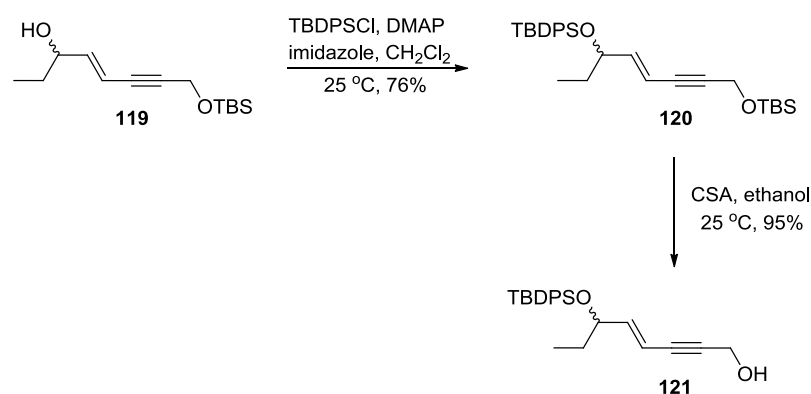
Scheme 2.14: Synthesis of compound **118**.

The aldehyde **118** was then treated with 2.3 equivalents of ethylmagnesium bromide at $-45\text{ }^{\circ}\text{C}$ to afford the alcohol **119** as a racemic mixture in 81% yield (Scheme 2.15). The racemic alcohol was used in the proceeding steps, with the (*R*)-alcohol of **119** planned to be synthesised at a later stage. The ^1H NMR spectrum of the product showed a new resonance at 4.07 ppm that was ascribed to the methine hydrogen of the carbon bearing the hydroxyl group. Two new signals at 1.55 (2 H) and 0.94 (3 H) ppm were also observed in the ^1H NMR spectrum. These were assigned to the methylene and methyl hydrogens of the ethyl group. Elemental analysis of the product was also consistent with the molecular formula of compound **119**.



Scheme 2.15: Synthesis of the alcohol **119**.

A two step procedure was developed to prepare compound **121** from compound **119** (Scheme 2.16). This involved swapping the silyl protecting group from the primary alcohol to the secondary alcohol. To protect the secondary alcohol, a TBDPS group was chosen. TBDPS is stable under mildly acidic conditions, thus allowing the TBS on the primary alcohol to be removed without deprotecting the secondary alcohol. The primary alcohol could then be converted into a bromo substituent in the subsequent step.



Scheme 2.16: Preparation of compound **121**.

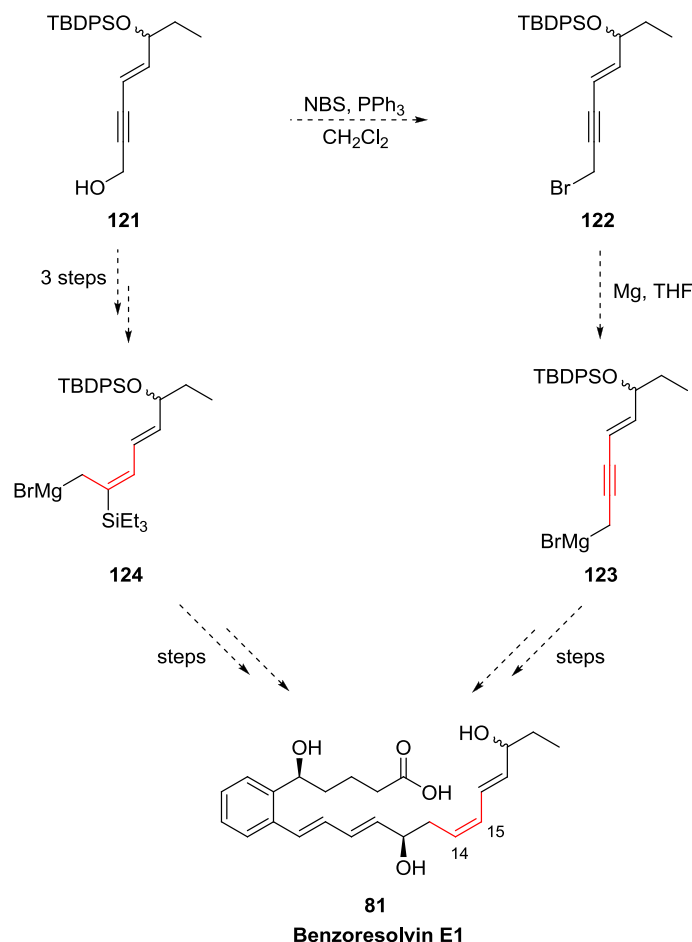
Treating the alcohol **119** with TBDPSCl, DMAP and imidazole gave compound **120** in 76% yield (Scheme 2.16). The ^1H NMR spectrum of the product showed two new multiplets between 7.38–7.63 ppm with an overall integration of ten hydrogens. These signals were ascribed to the aromatic hydrogens of the TBDPS group. The IR spectrum of the product showed the disappearance of the alcohol peak at 3398 cm^{-1} which supported the silylation of the secondary alcohol.

Compound **120** was then treated with a catalytic amount of CSA in ethanol at room temperature. This gave the alcohol **121** in 95% yield (Scheme 2.16). The ^1H NMR spectrum of the product showed two multiplets between 7.39–7.65 ppm that were ascribed to the aromatic signals of the TBDPS group. This suggests that the protecting group on the secondary alcohol was not removed. The disappearance of the two signals at 0.92 and 0.13 ppm in the ^1H NMR spectrum was also noted. These were ascribed to the TBS methyl groups of compound **120**. The IR spectrum showed a new peak at 3402 cm^{-1} that was assigned to the primary alcohol. This is further evidence for the removal of the TBS group.

2.5 Hydrosilylation approach

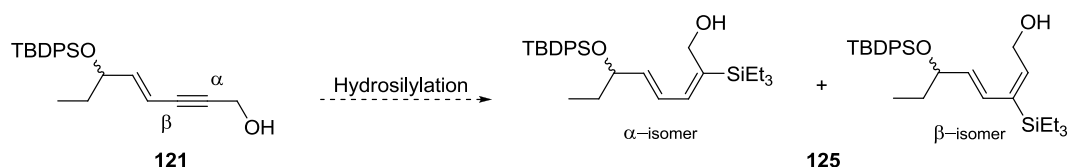
A key feature of benzoiresolvin E1 **81** is the 14*Z*-alkene (Scheme 2.17). In the synthesis of resolvin E1 developed by Petasis and Allard,^{180,182} the *Z*-alkene was prepared by reducing the alkyne with a Zn(Cu/Ag) amalgam. The reduction was conducted at the end of the synthesis because the *Z*-alkene could isomerise to the more favourable *E*-alkene. In the system shown in Scheme 2.17, two different pathways could afford the 14*Z*-alkene of benzoiresolvin E1. The primary alcohol of the key intermediate **121** could be converted into a bromo group via an Appel reaction, followed by the reaction with magnesium turnings to give the propargylic Grignard reagent **123**. This compound could be added to the aldehyde **86** to give the key intermediate **85** shown in Scheme 2.01. Following the same method as Allard,¹⁸² the alkyne could be reduced in the last step of the synthesis to form the 14*Z*-alkene. Alternatively, compound **121** could be converted into **124** in 3 steps (Scheme 2.17). The key step in this route is the silylation of the alkyne to afford an alkene. The bulky triethylsilyl group of **124** would improve the stability of the alkene, preventing isomerisation at this position. This approach allows the alkyne to be reduced at an

earlier stage in the synthesis, with the removal of the silyl group affording the 14Z-alkene at a later stage.



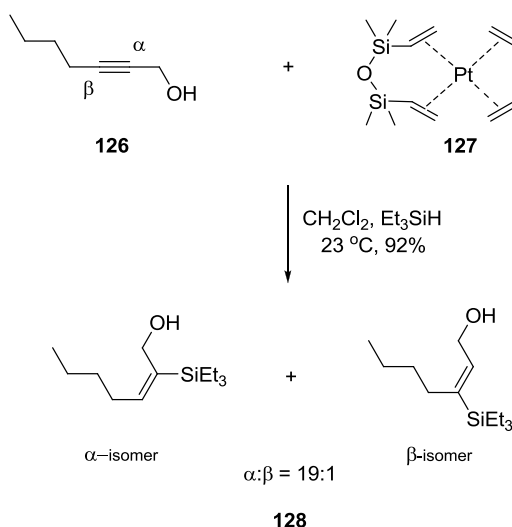
Scheme 2.17: Two possible pathways to prepare the 14Z-alkene of benzoeresolvin E1.

Focusing on the latter approach, the hydrosilylation of the alkyne **121** could give two regioisomers, the α -isomer and the β -isomer (Scheme 2.18). Since the silyl group is removed at a later stage in the synthesis, either isomer could be used in the next step. However, only one isomer was wanted. This would avoid preparing future compounds as a mixture of isomers that have complex NMR spectra.



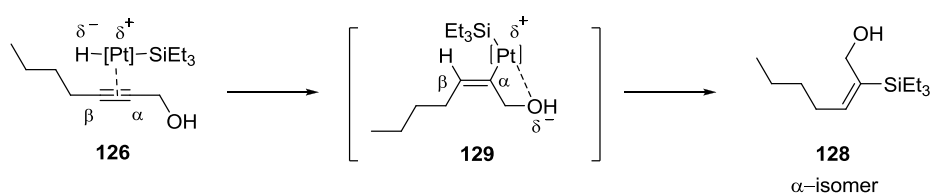
Scheme 2.18: Regioisomers of compound **125**.

A study by Rooke and Ferreira has shown that compounds with propargylic alcohols undergo hydrosilylation to give the α -isomer in high yields.²⁰⁹ One example of this was illustrated in Scheme 2.19.²⁰⁹ Using Karstedt's catalyst **127** and triethylsilane, Rooke and Ferreira prepared compound **128** from compound **126** in a 19:1 ratio in favour of the α -isomer.²⁰⁹



Scheme 2.19: Rooke and Ferreira's procedure for the hydrosilylation of the alkyne **126**.²⁰⁹

The high selectivity for the α -isomer was rationalised by the coordinative effects of the propargylic alcohol. Rooke and Ferreira have suggested that the propargylic alcohol could coordinate with platinum, as shown in the intermediate **129** (Scheme 2.20).²⁰⁹ This hydrogen bonding interaction directs the triethylsilyl group towards the α -position.



Scheme 2.20: Hydrogen bonded platinum intermediate **129**.

Adapting the procedure by Rooke and Ferreira, the alcohol **121** was treated with 1.1 equivalents of triethylsilane and Karstedt's catalyst (6 mol%) in anhydrous tetrahydrofuran (Table 2.03, entry 1). After stirring the reaction mixture at room temperature for 15 hours, compound **125** was afforded as a mixture of regioisomers in 78% yield. The ^1H NMR spectrum of the crude reaction mixture showed a 65:35

ratio of the α and β -isomers. The key vinylic signals are shown in Figure 2.05 and were assigned using a 2D-COSY NMR experiment.

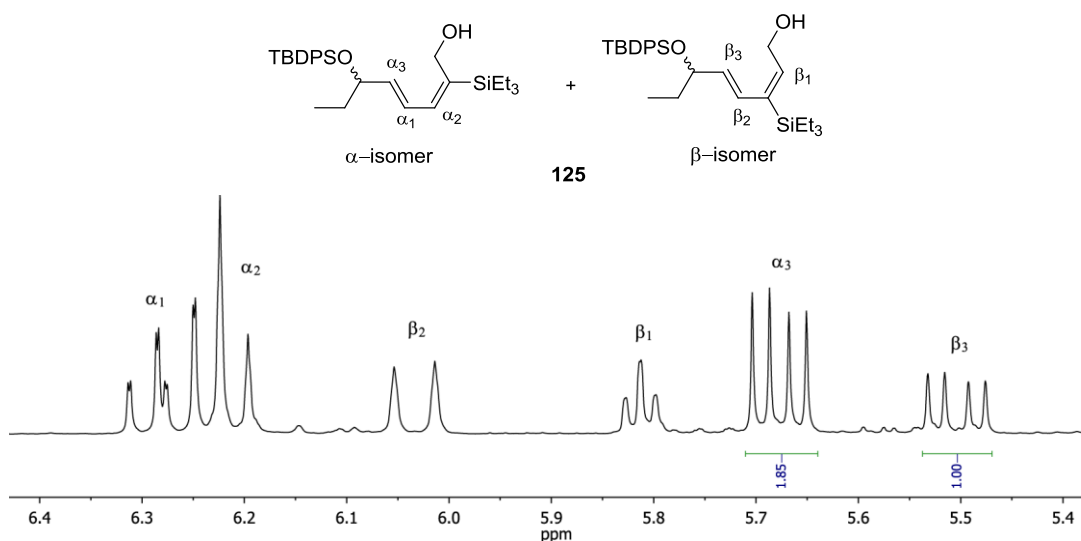
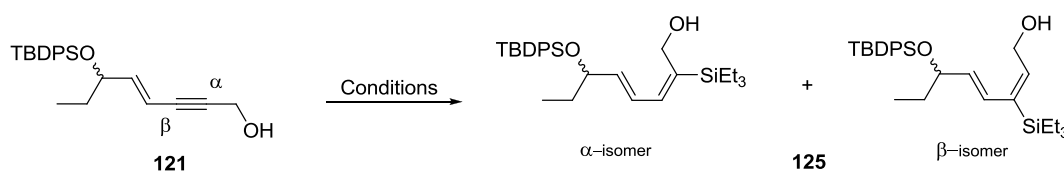


Figure 2.05: ^1H NMR spectrum of the alcohol **125** in CDCl_3 (5.40–6.45 ppm).

Changing the solvent to dichloromethane gave a similar result (Table 2.03, entry 2). The reaction was also repeated with hexachloroplatinic acid, giving compound **125** in 30% yield as a 65:35 mixture of regiosomers (Table 2.03, entry 3). The low yield for this reaction was rationalised by the acid mediated decomposition of the allylic alcohol. Unfortunately, attempts to separate the α and β -isomers via column chromatography were unsuccessful. In view of this, the reduction of the alkyne was postponed to a later stage in the synthesis.

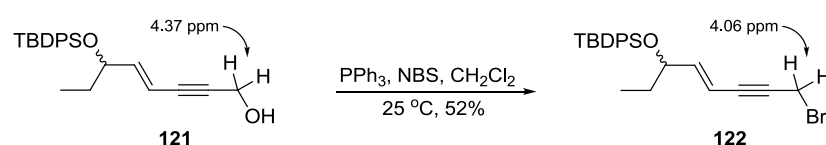
Table 2.03: Hydrosilylation of compound **121**.



Entry	Conditions	α / β *	Yield
1	Karstedt's catalyst (6 mol %), SiEt_3H (1.1 eq.), THF, 25 °C, 15 hrs	65:35	78%
2	Karstedt's catalyst (6 mol %), SiEt_3H (1.1 eq.), CH_2Cl_2 , 25 °C, 15 hrs	64:36	76%
3	$\text{H}_2\text{PtCl}_6 \cdot 6 \text{H}_2\text{O}$ (6 mol%), SiEt_3H (1.1 eq.), THF, 25 °C, 15 hrs	65:35	30%

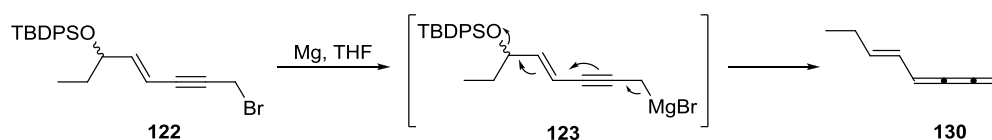
* Based on the ^1H NMR spectrum.

Focusing on the synthesis of the propargylic Grignard reagent **123** shown in Scheme 2.17, the primary alcohol of **121** was converted into a bromide via an Appel reaction. Treatment of compound **121** with *N*-bromosuccinimide and triphenylphosphine at room temperature afforded the bromide **122** in 52% yield (Scheme 2.21). The ^1H NMR spectrum showed a new resonance at 4.06 ppm with an integration of two hydrogens. This was consistent with the chemical shift expected for the hydrogens at the propargylic position.²¹⁰ The high resolution mass spectrum of the product also gave a molecular ion ($m/z = 441.1254 [\text{M}^+]$) that was congruent with the formula required for $\text{C}_{24}\text{H}_{29}\text{OBrSi}$.



Scheme 2.21: Preparation of the bromide **122**.

To prepare the Grignard reagent **123**, compound **122** in anhydrous tetrahydrofuran was treated with magnesium turnings at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. After this time, the mixture turned black. An aliquot of the reaction mixture was quenched with D_2O and extracted with CDCl_3 . The ^1H NMR spectrum showed a cluster of signals between 5.50–6.30 ppm and 0.20–1.50 ppm that could be assigned to vinylic and aliphatic hydrogens while the aromatic resonances between 7.39–7.66 ppm that were ascribed to the TBDPS group had disappeared. A possible mode of decomposition is shown in Scheme 2.22. The Grignard reagent **123** could eliminate TBDPSOMgBr to give the highly reactive cumulene **130**. This compound could undergo a series of unwanted reactions, leading to decomposition. To prevent the rearrangement of compound **123**, the reaction mixture was cooled to $-84\text{ }^\circ\text{C}$ upon initiation of the Grignard. Unfortunately, this also led to degradation.



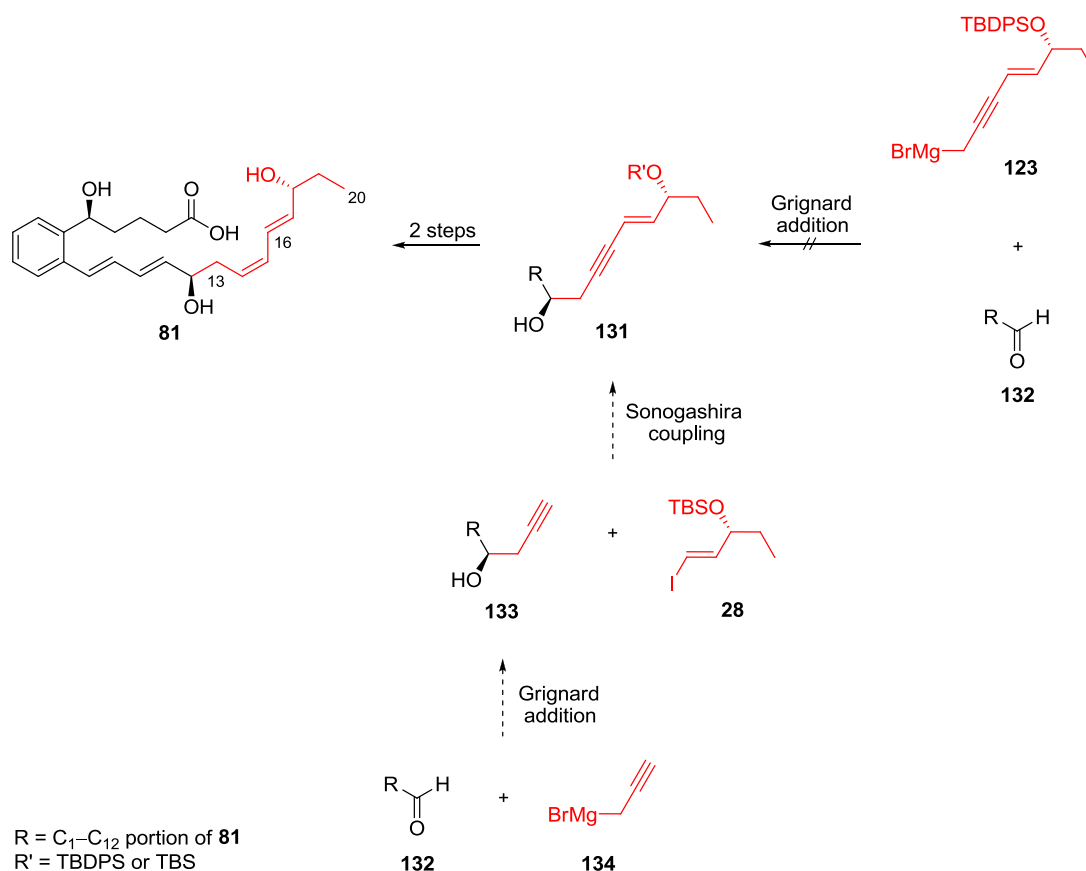
Scheme 2.22: Postulated rearrangement of the Grignard reagent **123**.

Chapter 3

Revised Strategy for Benzoiresolvin E1

3.1 Revised synthesis of the terminal chain

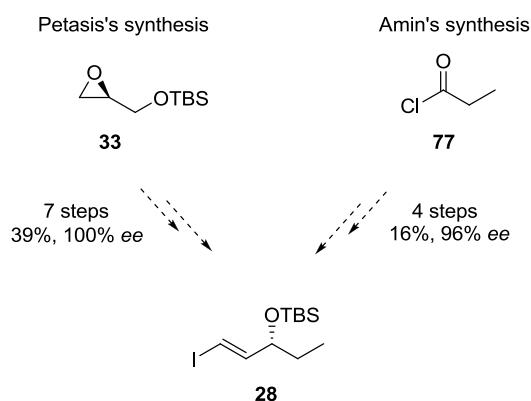
As the proposed Grignard **123** underwent an unexpected elimination reaction (Scheme 2.21), a stepwise procedure was developed. The Grignard reagent **123** could be segmented into two smaller compounds, propargylmagnesium bromide **134** and the iodide **28** (Scheme 3.01). The latter compound would form the C₁₆–C₂₀ terminal chain of benzoiresolvin E1. The aldehyde **132** could be treated with propargylmagnesium bromide **134** to afford the alcohol **133**. This compound could undergo a Sonogashira reaction with the iodide **28** to give the enyne portion of the target compound. The final steps in the proposed synthesis involved the reduction of the alkyne to give the 14Z-alkene and removal of the silyl protecting group (Scheme 3.01).



Scheme 3.01: Revised pathway for the preparation of the C₁₃–C₂₀ terminal chain.

3.2 Preparation of the C₁₆–C₂₀ portion of benzoeresolvin E1

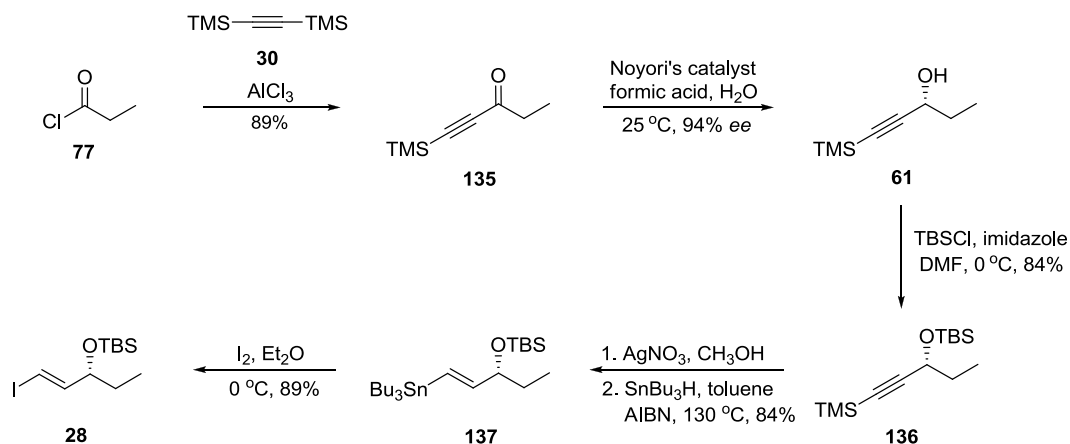
Five syntheses have been reported for compound **28**.^{180,182,185,211,212} The synthesis described by Petasis afforded **28** in 39% yield in 7 steps starting from glycidol **33** (Scheme 1.05).¹⁸⁰ This was the same method used by Allard (Scheme 1.16).¹⁸² Using a chiral pool strategy, the target compound **28** was prepared in 100% *ee*. The drawback of this method is that the starting material is expensive (\$47.50/g, Sigma-Aldrich).²¹³ Thus, large scale production of **28** using this pathway is not practical. Furthermore, the antepenultimate step in the synthesis involved a Takai olefination (Scheme 1.05). This reaction has been reported to give unreliable yields of compound **28**.¹⁸⁰ The third synthetic pathway was devised by Amin (Scheme 1.19).¹⁸⁵ Starting from propionyl chloride **77**, the iodide **28** was afforded in 16% yield in 4 steps. Unlike the starting material used by Petasis, propionyl chloride is cheap (\$25.00/25 g, Sigma-Aldrich).²¹³ This makes the preparation of the iodide **28** viable for large scale production. The (*R*)-alcohol of **28** was also formed with high enantiomeric purity. This was achieved via an asymmetric reduction reaction using (*S*)-CBS catalyst and BH₃•DMS to give the (*R*)-enantiomer in 96% *ee* (Scheme 1.19).



Scheme 3.02: Petasis and Amin's procedures for the preparation of compound **28**.^{180,185}

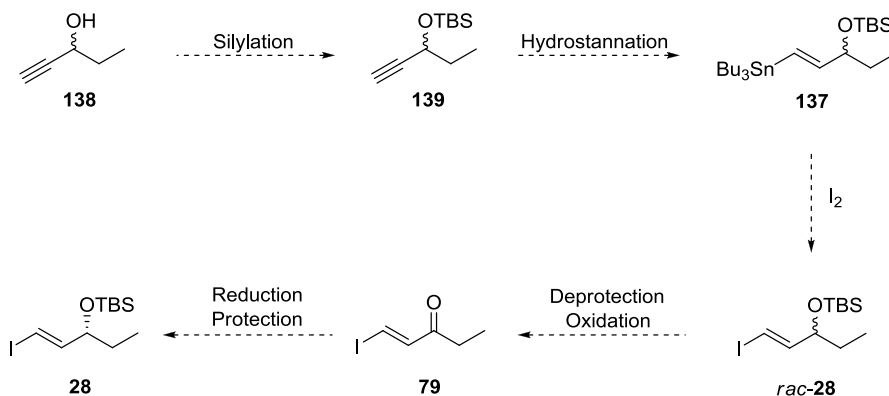
The fourth and fifth routes to prepare the iodide **28** were reported by Rodriquez and Fumie.²¹¹⁻²¹² Both pathways use the same hydrostannation strategy. Focusing on the method developed by Rodriquez,²¹¹ the target compound was synthesised in 56% yield and 94% *ee* in 6 steps starting from propionyl chloride **77** (Scheme 3.03). The key steps in the synthesis were the hydrostannation of the alkyne **136** using

tributyltin hydride and AIBN, followed by a reaction with molecular iodine to afford the vinylic iodide moiety of **28**.



Scheme 3.03: Rodriguez's synthesis of compound **28**.²¹¹

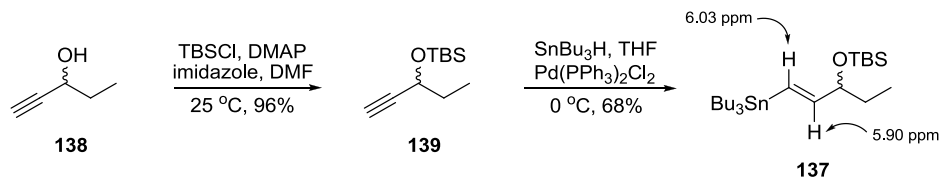
The iodide **28** could be prepared by adapting the reactions used by Amin and Rodriguez.^{185,211} Combining these synthetic pathways could give the target compound in a higher yield over a similar number of steps. In the planned synthesis, the target compound could be synthesised in 7 steps starting from 1-pentyn-3-ol **138** (Scheme 3.04). Following the last 2 steps reported by Rodriguez,²¹¹ hydrostannation of the alkyne **139** could furnish the stannane **137** while treatment of this compound with iodine could give *rac*-**28**. Removal of the silyl group followed by oxidation of the allylic alcohol could then afford the ketone **79** in 2 steps. Using the asymmetric reduction reaction reported by Amin,¹⁸⁵ the ketone **79** could be reduced to give the enantiomerically pure (*R*)-alcohol, followed by TBS protection of the alcohol to afford the iodide **28**.



Scheme 3.04: Proposed synthesis of the iodide **28**.

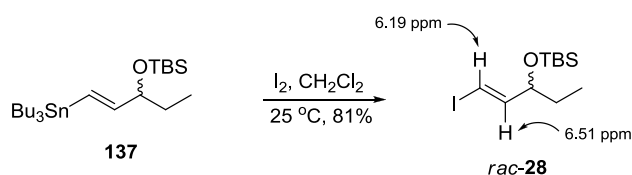
The silyl ether **139** was prepared in 96% yield from 1-pentyn-3-ol **138** using TBSCl, imidazole and DMAP (Scheme 3.05).²¹¹ Following the same conditions reported by Rodriquez,²¹¹ compound **139** was heated under reflux with 1.1 equivalents of tributyltin hydride, a catalytic amount of AIBN and toluene. The ¹H NMR spectrum of the crude reaction mixture after 2 hours showed all three possible isomers. This was inconsistent with the findings made by Rodriquez.²¹¹

In light of this result, milder conditions for the hydrostannation reaction were tested. Following the procedure described by Gallagher and co-workers,²¹⁴ the silyl ether **139** was treated with 1.1 equivalents of tributyltin hydride and a catalytic amount of Pd(PPh₃)₂Cl₂. This afforded the stannane **137** in 68% yield as the sole product (Scheme 3.05). The ¹H NMR spectrum of the product showed the appearance of three multiplets at 1.47–1.52, 1.25–1.36 and 0.86–0.94 ppm. These signals were ascribed to the butyl chain of the stannane. The ¹H NMR spectrum also showed two resonances at 6.03 and 5.90 ppm that were assigned to the vinylic hydrogens. These hydrogens have a common coupling constant of 19.1 Hz which supports the *E*-alkene of compound **137**.



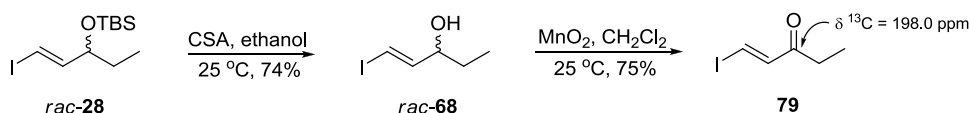
Scheme 3.05: Preparation of the stannane **137**.

The stannane **137** was stirred in a solution of iodine and anhydrous ether at room temperature to furnish *rac*-**28** in 81% yield (Scheme 3.06). Two new signals were observed at 6.51 and 6.19 ppm in the ¹H NMR spectrum. These were attributed to the vinylic hydrogens. These hydrogens have a common coupling constant of 14.4 Hz which is consistent with the *E*-alkene of *rac*-**28**.²¹¹



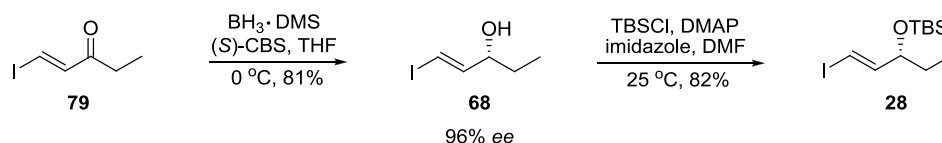
Scheme 3.06: Synthesis of *rac*-**28**.

To remove the TBS group, compound **28** was treated with a catalytic amount of CSA in ethanol at room temperature. This gave the *rac*-alcohol **68** in 74% yield (Scheme 3.07). The allylic alcohol was converted into a ketone using activated manganese dioxide to afford compound **79** in 75% yield. The ^{13}C NMR spectrum of the product showed a new resonance at 198.0 ppm ascribed to the ketone. This was consistent with the signal reported in the literature.¹⁸⁵



Scheme 3.07: Preparation of the ketone **79**.

Following the same procedure reported by Amin,¹⁸⁵ the ketone **79** in anhydrous tetrahydrofuran was treated with (*S*)-CBS catalyst (10 mol%) and 0.6 equivalents of $\text{BH}_3\cdot\text{DMS}$ (Scheme 3.08). After stirring the reaction mixture for 3 hours at 0 °C, compound **68** was afforded in 81% yield. This was lower than the 87% yield reported in the literature.²¹⁷ The ^1H NMR spectrum of the product matched the ^1H NMR spectrum of *rac*-alcohol **68**. The specific rotation of compound **68** was -0.44 ($c = 1.00$, CH_3OH). At the same temperature, Amin reported the specific rotation of the enantiomerically pure (*R*)-alcohol to be -0.46° ($c = 1.50$, CH_3OH).¹⁸⁵ This suggests that the (*R*)-alcohol of **68** was prepared in 96% *ee*. Subsequent treatment of this compound with TBSCl, DMAP and imidazole gave the target compound **28** in 82% yield.



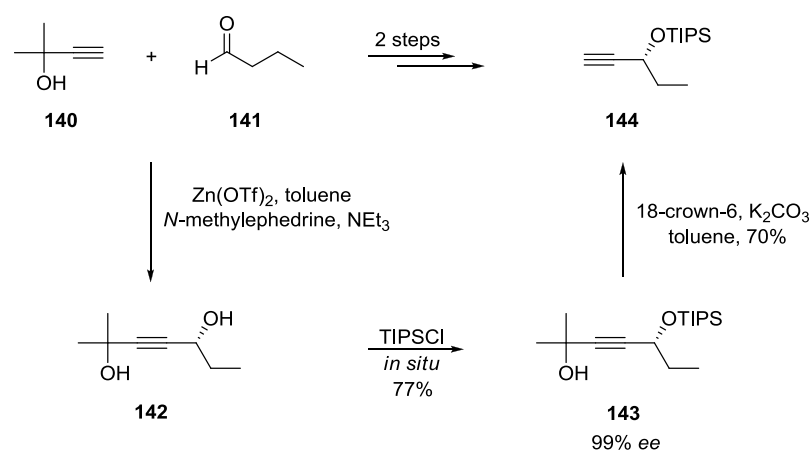
Scheme 3.08: Synthesis of the iodide **28**.

3.3 Scalable synthesis of the iodide **28**

The iodide **28** was prepared in 20% yield in 7 steps from the pathway shown in Scheme 3.04. This was higher than the yield obtained by Amin.¹⁸⁵ To prepare compound **28** on a large scale, a modified synthesis starting from propionaldehyde **60** and 2-methyl-3-butyn-2-ol **140** was explored. These compounds are cheap,

making large quantities of the iodide **28** feasible. Propionaldehyde **60** can be purchased for \$0.34/g²¹⁵ while 2-methyl-3-butyn-2-ol **141** costs \$3/kg.²¹⁶

Using butyraldehyde **141** and 2-methyl-3-butyn-2-ol **140**, Boyall and co-workers reported an efficient 2 step synthesis for alkyne **144** (Scheme 3.09).²¹⁶ The first step involved the asymmetric addition of **140** to compound **141** using zinc trifluoromethanesulfonate, triethylamine and (-)-*N*-methylephedrine followed by protection of the secondary alcohol with a TIPS group. This afforded compound **143** in 77% yield and 99% *ee*. Compound **143** was then treated with 18-crown-6 and potassium carbonate to furnish the alkyne **144** in 70% yield.

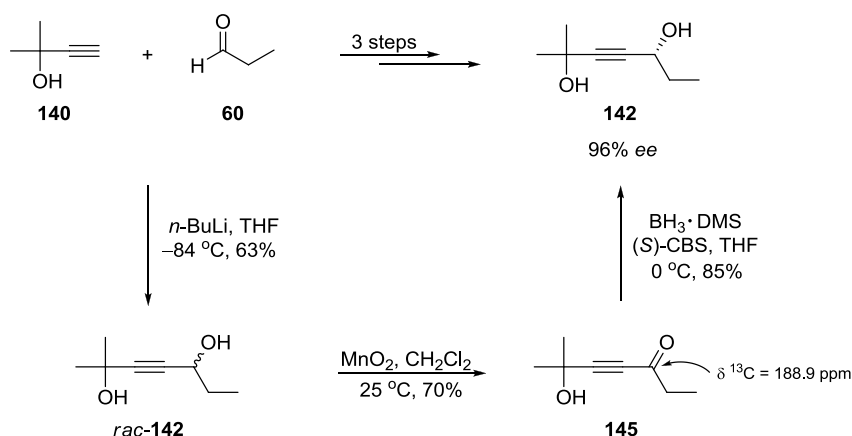


Scheme 3.09: Boyall's synthesis of the alkyne **144**.²¹⁶

Compound **144** is similar to the silyl ether **139**, which is a key intermediate in the previously developed synthesis of compound **28** (Scheme 3.04). A pathway similar to Boyall's approach could be used to prepare the (*R*)-enantiomer of the silyl ether **139**. This pathway would intersect the synthesis in Scheme 3.04, providing an alternate route to the iodide fragment **28**. Since (-)-*N*-methylephedrine cannot be purchased in Australia, the enantiomerically pure diol **142** could not be prepared in one step from propionaldehyde **60** and 2-methyl-3-butyn-2-ol **140**. As such, a longer synthetic route was planned (Scheme 3.10). This involved the addition of 2-methyl-3-butyn-2-ol **140** to propionaldehyde **60**, followed by the oxidation of *rac*-**142** and the reduction of the ketone **145** (Scheme 3.10).

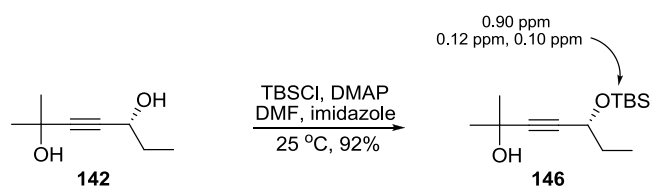
2-Methyl-3-butyn-2-ol **140** was treated with *n*-BuLi to form a lithium acetylide. This was added dropwise to a solution of propionaldehyde **60** in anhydrous tetrahydrofuran at $-84\text{ }^\circ\text{C}$ to afford *rac*-**142** in 63% yield. The crude reaction mixture

was dissolved in anhydrous dichloromethane and stirred at room temperature with activated manganese dioxide to furnish the ketone **145** in 70% yield (Scheme 3.10). The ^{13}C NMR spectrum of the product showed the appearance of a resonance at 188.9 ppm that was assigned to the ketone while the ^1H NMR spectrum was consistent with the spectroscopic data reported in the literature.²¹⁷ Using the same conditions outlined in Scheme 3.08, the ketone was reduced with (*S*)-CBS catalyst (10 mol%) and $\text{BH}_3\cdot\text{DMS}$ (Scheme 3.10). This afforded the (*R*)-alcohol **142** in 85% yield and 96% *ee*. The absolute configuration of the alcohol was determined by comparing the specific rotation of the desilylated target fragment **68**, prepared in the subsequent steps, to the value given in the literature.¹⁸⁵



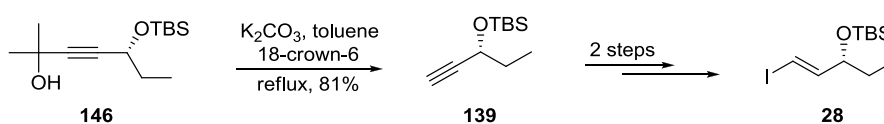
Scheme 3.10: Scalable pathway for the synthesis of the (*R*)-alcohol **142**.

The secondary alcohol was then selectively protected using TBSCl, imidazole and DMAP at 25 °C (Scheme 3.11). This gave compound **146** in 92% yield. The ^1H NMR spectrum of the product showed three new singlets at 0.90 (9 H), 0.12 (3 H) and 0.10 (3 H) ppm that were ascribed to the methyl hydrogens of the TBS group. This suggests that only one alcohol was silylated. Furthermore, the ^1H NMR spectrum of the product was almost identical to the ^1H NMR spectrum of compound **143**.²¹⁶ This is the best evidence for the silylation of the secondary alcohol.



Scheme 3.11: Silylation of the (*R*)-alcohol **142**.

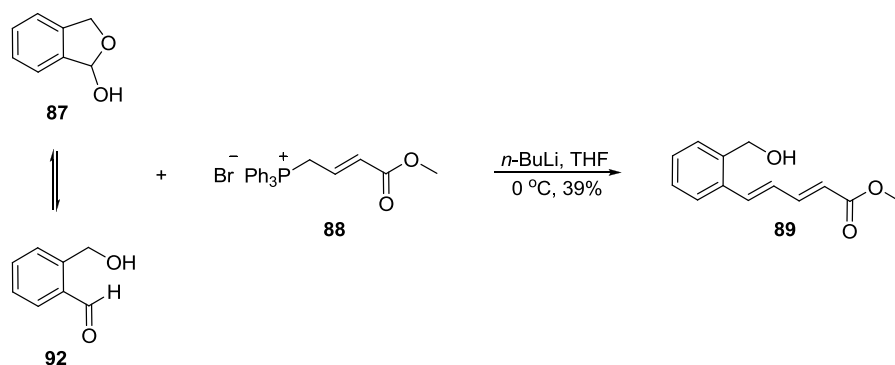
Following the procedure developed by Boyall and co-workers,²¹⁶ compound **146** was heated under reflux in toluene with potassium carbonate and 18-crown-6 (Scheme 3.12). After 5 hours, the silyl ether **139** was afforded in 81% yield. 18-Crown-6 was used to coordinate the potassium cation. This allowed the carbonate anion to deprotonate the tertiary alcohol, thus facilitating the fragmentation of compound **146** into the product and acetone. The specific rotation of the silyl ether **139** was -0.40 ($c = 1.00$, CHCl_3). This suggests that the product had not racemised under these conditions. Compound **139** intersects the synthesis shown in Scheme 3.05 and was converted into the target fragment **28** in 2 steps following the hydrostannation approach.



Scheme 3.12: Preparation of the key intermediate **28**.

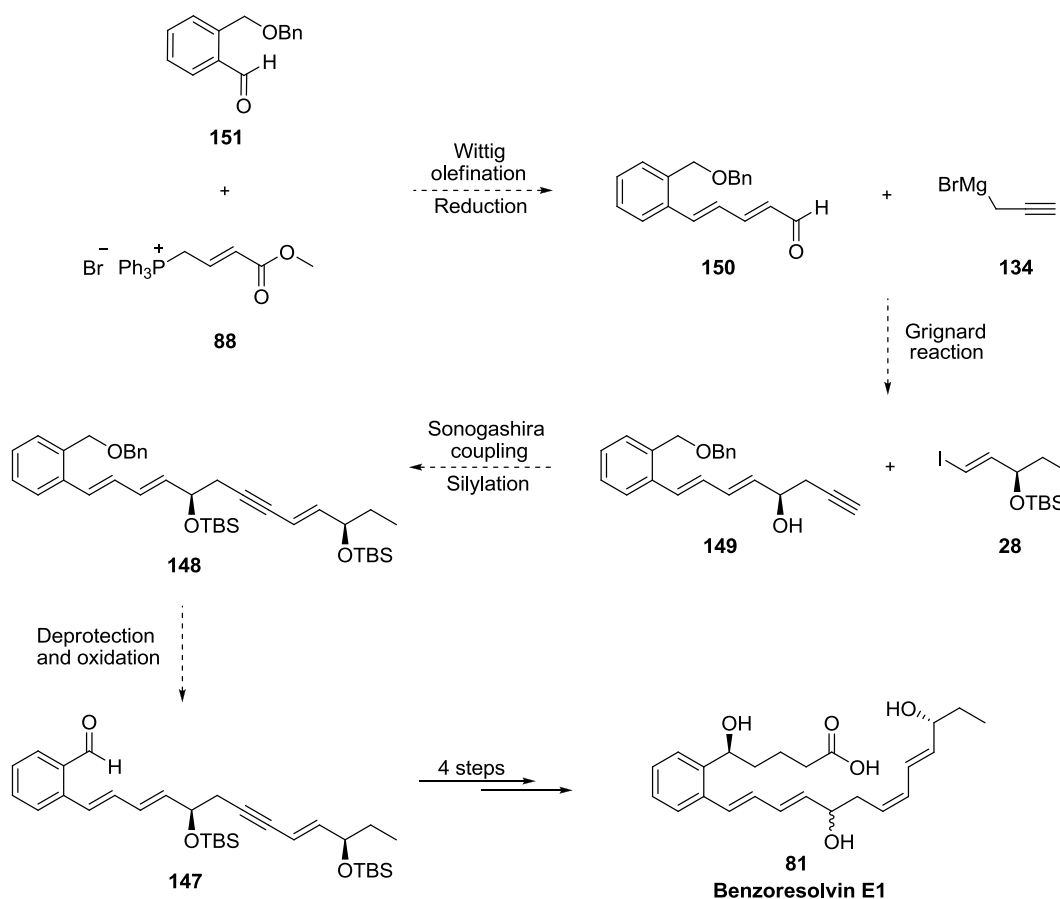
3.4 Proposed synthesis of compound **147**

Having synthesised the C_{16} – C_{20} portion of benzo-resolvin E1, the Wittig olefination step described in Scheme 3.13 was revisited. Low yields of the olefination product were observed when the lactol **87** was reacted with the phosphonium salt **88**. The equilibration of the lactol **87** with the aldehyde **92** could be responsible for the poor yields. To avoid this, the benzyl alcohol of compound **92** was protected. The protecting group chosen was a benzyl group. The benzyl ether could be deprotected in the presence of silyl ethers via single electron reductive conditions.²¹⁸⁻²¹⁹ This is important in the case of compound **148** which has two silyl protected allylic alcohols (Scheme 3.14). This approach would allow easy access to the benzyl alcohol at a later stage in the synthesis.



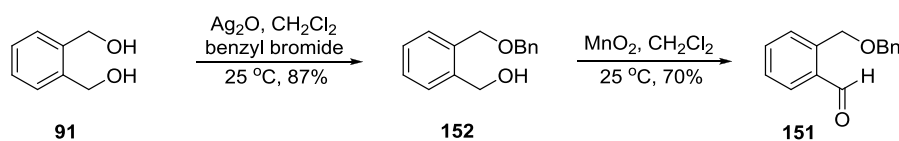
Scheme 3.13: Wittig olefination of the lactol **87**.

The revised synthesis is shown in Scheme 3.14. The key intermediate in this route was the aldehyde **147**. Benzo-resolvin E1 could be prepared from this compound in 4 steps. The aldehyde **147** could be synthesised from compound **148** by removing the benzyl group followed by oxidation of the alcohol. Compound **148** could be made by a Sonogashira reaction between the alkyne **149** and the iodide **28** followed by silyl group protection of the allylic alcohol. The terminal alkyne of **149** could be installed by the addition of propargylmagnesium bromide **134** to the aldehyde **150**. Finally, a Wittig olefination with the aldehyde **151** and the phosphonium salt **88** followed by reduction of the methyl ester could give the aldehyde **150**.



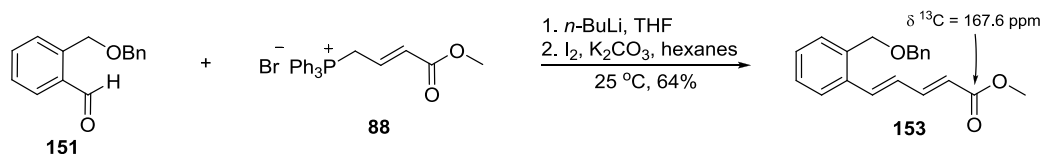
Scheme 3.14: Planned synthesis of compound **147**.

Using the method described by Bouzide and Sauve,²²⁰ the aldehyde **151** was synthesised in 2 steps (Scheme 3.15). Monobenylation of the diol **91** with benzyl bromide afforded compound **152** in 87% yield. The reaction proceeded with excellent selectivity towards the monobenzylation product, giving only trace amounts of the dibenzylated compound. This selectivity was achieved by using silver oxide. The silver oxide coordinates to the two alcohols, making one of the hydrogens labile.²²⁰ This increases the nucleophilicity of one of the alcohols, facilitating the S_N2 reaction with benzyl bromide. The remaining hydroxyl proton is difficult to remove since it remains coordinated to the silver oxide. Thus, the addition of a second benzyl group is less likely to occur. Compound **152** was then oxidised using activated manganese dioxide to furnish the aldehyde **151** in 70% yield (Scheme 3.15).



Scheme 3.15: Preparation of the aldehyde **151**.

A Wittig olefination was attempted to form compound **153**. Treatment of the phosphonium salt **88** with the aldehyde **151** in anhydrous tetrahydrofuran at 25 °C gave the product **153** as 1:1 mixture of the 4*E* and 4*Z* stereoisomers (Scheme 3.16). Complete isomerisation of the mixture to the desired 4*E*-isomer was achieved using catalytic amounts of iodine and potassium carbonate in hexanes. Potassium carbonate served to neutralise trace amounts of HI formed which could lead to decomposition of the newly formed benzodiene.



Scheme 3.16: Wittig olefination with the aldehyde **151** and compound **88**.

The ^1H NMR spectrum of the product showed three vinylic signals at 7.18, 6.83 and 6.00 ppm along with one vinylic signal embedded amongst the aromatic resonances at 7.43 ppm (Figure 3.01). The two signals at 7.43 and 6.00 ppm have a common coupling constant of 15.3 Hz while the signals at 7.18 and 6.83 ppm share a coupling constant of 15.5 Hz. This suggests that the product has two *E*-alkenes. A resonance at 167.6 ppm was observed in the ^{13}C NMR spectrum while an absorbance at 1713 cm^{-1} was shown in the IR spectrum. These signals were ascribed to the carbonyl group of the methyl ester.

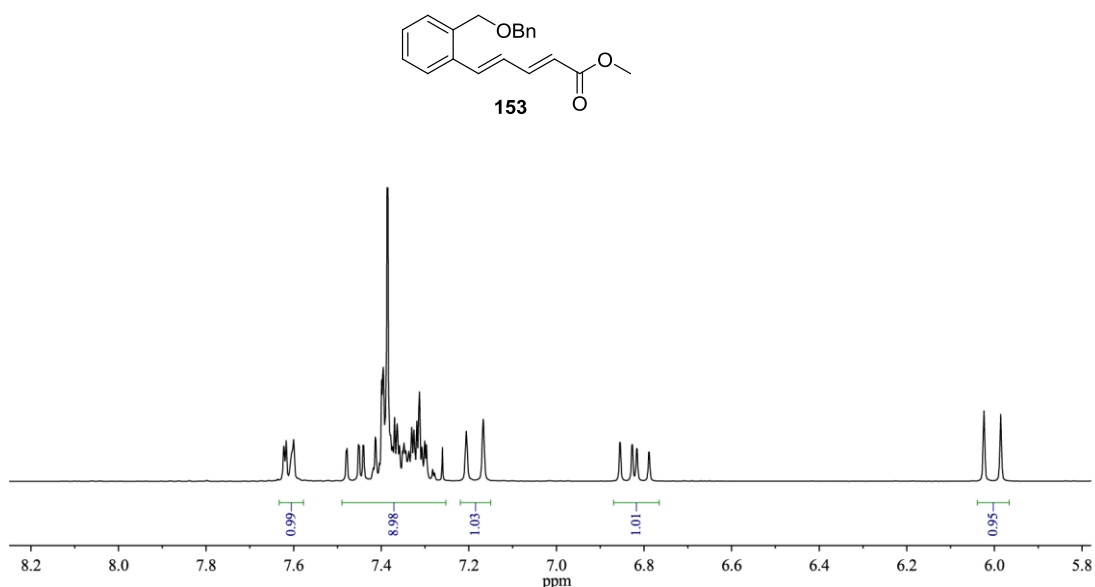
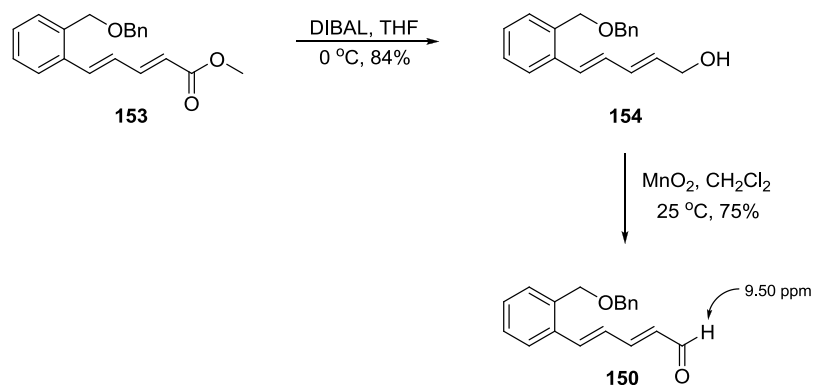


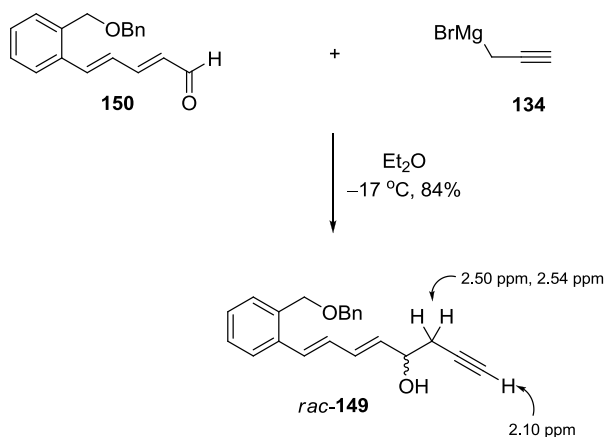
Figure 3.01: ^1H NMR spectrum of compound **153** in CDCl_3 (5.80–8.20 ppm).

The ester **153** was reduced to the alcohol **154** using two equivalents of DIBAL at 0 °C (Scheme 3.17). The product was then treated with activated manganese dioxide to afford the aldehyde **150** in 63% yield in two steps. A new signal at 9.50 ppm in the ^1H NMR spectrum was observed. This was assigned to the hydrogen of the aldehyde.



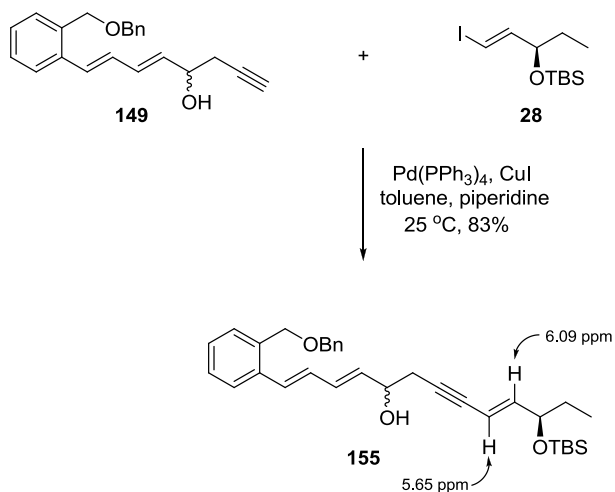
Scheme 3.17: Preparation of the aldehyde **150**.

With the aldehyde **150** in hand, the next step was to install the terminal alkyne. This could be achieved by treating the aldehyde **150** with propargylmagnesium bromide **134**. To prepare propargylmagnesium bromide, propargyl bromide in anhydrous ether was treated with magnesium turnings and mercury(I) chloride at 25 °C.²²¹ Complete consumption of the starting material was achieved after 10 minutes, giving the Grignard reagent **134**. The mercury(I) chloride additive was important for the initiation of the Grignard, with mercury forming an amalgam with the magnesium to activate its surface.²²² The aldehyde **150** was then treated with propargylmagnesium bromide **134** at -17 °C (Scheme 3.18). The product *rac*-**149** was afforded in 84% yield. The addition of the propargyl moiety was inferred by the mass spectrum ($m/z = 341.1514$ $[\text{M}+23 (\text{Na})]^+$), which was consistent with the molecular formula required for compound **149**. The ^1H NMR spectrum of the product showed the appearance of two signals at 2.50 and 2.54 ppm that were ascribed to the diastereotopic propargylic hydrogens and a resonance at 2.10 ppm that was attributed to the acetylenic hydrogen. The ^{13}C NMR spectrum also showed three new resonances at 80.4, 71.2 and 27.8 ppm that were assigned to the three carbons of the propargyl group.



Scheme 3.18 Addition of propargylmagnesium bromide to the aldehyde **150**.

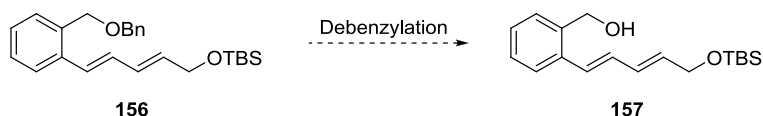
Having prepared *rac*-**149**, a Sonogashira reaction with compound **28** was investigated. Preparation of the (*R*)-alcohol of **149** was postponed to see if the subsequent steps were viable. The Sonogashira reaction was performed by treating *rac*-**149** and the iodide **28** with copper(I) iodide, piperidine and Pd(PPh₃)₄. The reaction proceeded smoothly, affording compound **155** in 83% yield as a mixture of diastereoisomers (Scheme 3.19). The product was confirmed by the disappearance of the acetylenic proton at 2.10 ppm in the ¹H NMR spectrum along with the appearance of two resonances at 6.09 and 5.65 ppm that could be ascribed to the two vinylic hydrogens. These signals have a common coupling constant of 15.8 Hz which is consistent with the *E*-alkene of the product. In addition, the molecular ion at $m/z = 539.2976$ [M+23 (Na)]⁺ was consistent with the molecular formula of compound **155**. Interestingly, both the ¹H NMR and ¹³C NMR spectra showed no clear distinction between the two newly formed diastereoisomers due to the large distance between the two stereocenters.



Scheme 3.19: Sonogashira reaction with compounds **149** and **28**.

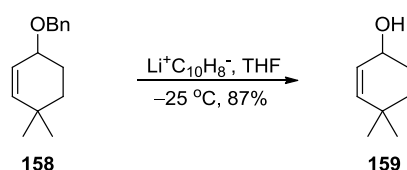
3.5 Removal of the benzyl group

Having successfully constructed the benzodiene and enyne portions of the target compound, attention was focused on deprotecting the benzyl alcohol. To investigate the ideal conditions to remove the benzyl group, the silyl ether **156** was used as a model compound (Scheme 3.20). This compound has a benzodiene and an allylic silyl ether similar to compound **155**.



Scheme 3.20: Debenzylation of the model compound **156**.

Removal of benzyl ethers using hydrogen and palladium on carbon is the most traditional method however this is not viable for a system such as compound **155** since the alkyne and the alkenes would also be reduced. Subsequently, a more condition specific approach using either lithium naphthalenide, sodium/ammonia or DIBAL was explored. Lithium naphthalenide is known to selectively cleave benzyl ethers attached to allylic and benzylic carbons.²²³⁻²²⁴ This is particularly important for compound **155** that has two benzyl groups either side of the ether. An example of this selectivity was reported by Liu and Yip.²²⁴ Using an excess of lithium naphthalenide, they were able to selectively remove the benzyl group in the presence of an allylic ether (Scheme 3.21).



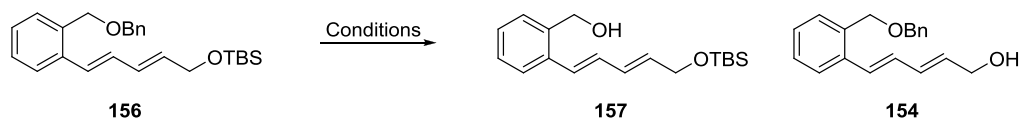
Scheme 3.21: Benzyl group deprotection of compound **158** devised by Liu and Yip.²²⁴

Following the same conditions reported by Liu and Yip,²²⁴ compound **156** in anhydrous tetrahydrofuran was treated with one equivalent of lithium naphthalenide at $-84\text{ }^\circ\text{C}$. No reaction was observed after 4 hours, as monitored by TLC (Table 3.01, entry 1). An increase in the number of equivalents of lithium naphthalenide along with increasing the reaction temperature to $0\text{ }^\circ\text{C}$ gave the same result (Table 3.01, entries 2, 3 and 4). The Birch reductive conditions outlined by Phillips were also

tested however this led to quantitative recovery of starting material. (Table 3.01, entries 5 and 6).²²³

DIBAL was then investigated in an attempt to cleave the benzyl ether. This reagent is commonly used to debenzylate oligosaccharides via a radical induced pathway.²²⁵ Following the conditions outlined by Pearce and Sinay,²²⁶ a solution of DIBAL (1 M in toluene) and compound **156** was stirred for 1 hour at room temperature. After this time, the formation of a new spot by TLC was noted (Table 3.01, entry 7). The ¹H NMR spectrum of the new compound showed the disappearance of the resonances at 0.83 and 0.00 ppm that are ascribed to the methyl hydrogens of the silyl group. Thus, the product was assigned as the allylic alcohol **154**. Heating the reaction mixture to 70 °C for 12 hours also gave compound **154** in 77% yield while heating the mixture to 140 °C in a sealed vessel led to decomposition (Table 3.01, entries 8 and 9).

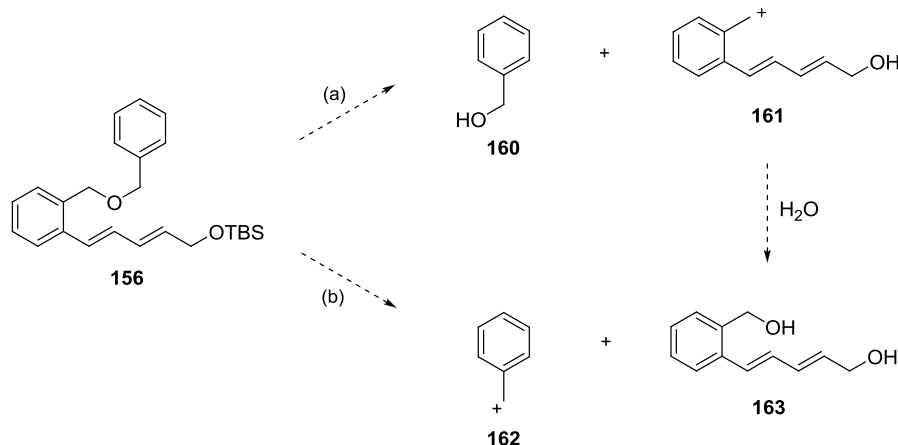
Table 3.01: Attempted debenzylation of compound **156** by single electron reductive conditions.



Entry	Conditions	Result
1	Li ⁺ C ₁₀ H ₈ ⁻ (1 eq.), THF, -84 °C, 4 hrs	no reaction
2	Li ⁺ C ₁₀ H ₈ ⁻ (3 eq.), THF, -84 °C, 4 hrs	no reaction
3	Li ⁺ C ₁₀ H ₈ ⁻ (6 eq.), THF, -84 °C, 4 hrs	no reaction
4	Li ⁺ C ₁₀ H ₈ ⁻ (6 eq.), THF, 0 °C, 4 hrs	no reaction
5	Na (6 eq.), NH ₃ , THF, -84 °C, 5 mins	no reaction
6	Na (6 eq.), NH ₃ , THF, -84 °C, 12 hrs	no reaction
7	DIBAL (150 eq.), 25 °C, 1 hr	154 (71%)
8	DIBAL (150 eq.), 70 °C, 12 hrs	154 (77%)
9	DIBAL (150 eq.), 140 °C, 12.5 hrs	decomposition

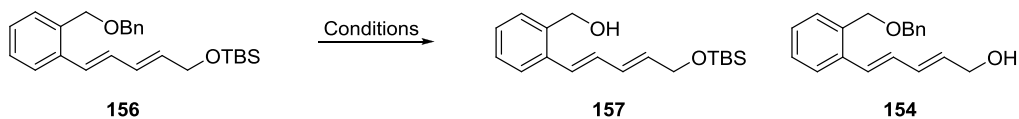
In light of these findings, a Lewis acid to mediate the debenzylation of compound **156** was trialled. Lewis acids such as TMSI, BF₃•OEt₂, CH₃AlCl₂, FeCl₃ and Zn(OTf)₂ are known to effectively cleave benzyl ethers via an S_N1 mechanism.²²⁷⁻²³⁰ They can also deprotect silylated alcohols. This would not be an issue for the real system as the silyl group could be reintroduced on the allylic alcohol at a later stage in the synthesis. Using this approach, it was anticipated that the benzyl ether could be cleaved at two different sites. Pathway (a) would give benzyl alcohol **160** and the

carbocation **161** while pathway (b) would afford the carbocation **162** and the target compound **163** (Scheme 3.22). Either pathway would give the benzyl alcohol, with hydrolysis of the carbocation **161** leading to the desired compound **163**.



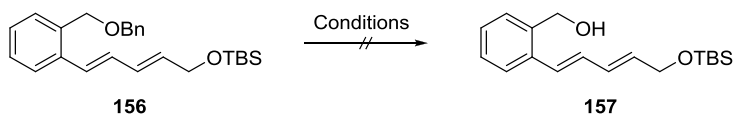
Scheme 3.22: Proposed pathways for the Lewis acid mediated cleavage of the benzyl ether **156**.

The first Lewis acid that was tested was trimethylsilyl iodide (TMSI). Initial attempts to deprotect compound **156** in dichloromethane at 0 °C led to decomposition, with only aliphatic signals in the ^1H NMR spectrum of the crude reaction mixture observed (Table 3.02, entry 1). Repeating the reaction at -84 °C and changing the solvent to acetonitrile gave the same result (Table 3.02, entries 2 and 3). Next, the Lewis acid $\text{BF}_3 \cdot \text{OEt}_2$ was trialled. Similar to entry 1, decomposition of **156** was observed when the compound was treated with an excess of $\text{BF}_3 \cdot \text{OEt}_2$ at 0 °C (Table 3.02, entry 4). When the reaction was cooled to -84 °C, complete consumption of the starting material was noted, with compound **154** isolated in 86% yield from the reaction mixture (Table 3.02, entry 5). Changing the Lewis acid to methyl aluminium dichloride gave the same outcome, with **154** afforded in 82% yield after stirring the reaction mixture for 1 hour at -45 °C (Table 3.02, entry 7).

Table 3.02: Attempted Lewis acid mediated debenzylation of compound **156**.

Entry	Conditions	Result
1	TMSI (1.3 eq.), CH ₂ Cl ₂ , 0 °C, 1.5 hrs	decomposition
2	TMSI (1.3 eq.), CH ₂ Cl ₂ , –84 °C, 1.5 hrs	decomposition
3	TMSI (1.3 eq.), MeCN, –84 °C, 1.5 hrs	decomposition
4	BF ₃ •OEt ₂ (5 eq.), CH ₂ Cl ₂ , 0 °C, 3 hrs	decomposition
5	BF ₃ •OEt ₂ (5 eq.), CH ₂ Cl ₂ , –84 °C, 3 hrs	154 (86%)
6	CH ₃ AlCl ₂ (1 M, 1.2 eq.), CH ₂ Cl ₂ , 0 °C, 1 hr	decomposition
7	CH ₃ AlCl ₂ (1 M, 1.2 eq.), CH ₂ Cl ₂ , –45 °C, 1 hr	154 (82%)

In view of these results, oxidative conditions were investigated. Reagents such as CrO₃, RuO₂ and DDQ have been shown to cleave benzyl ethers.²³¹⁻²³³ The most promising of these reagents is DDQ, which was used in Hirama's total synthesis of Ciguatoxin.²³⁴ Following the same conditions described by Hirama, compound **156** in anhydrous dichloromethane was treated with an excess of DDQ at 58 °C. The ¹H NMR spectrum of the crude reaction mixture was not promising, with only a cluster of resonances observed in the aliphatic region (Table 3.03, entry 1). When the reaction was repeated at room temperature using one equivalent of DDQ, a complex mixture of compounds was afforded (Table 3.03, entry 2). The ¹H NMR spectrum of the crude reaction mixture showed two singlets and two doublets between 9.60–10.30 ppm that are in the region expected for an aldehyde. Furthermore, a cluster of signals were observed between 6.30–7.90 ppm. These could be aromatic and vinylic hydrogens. Based on this information, the reaction mixture could be an assortment of isomeric dialdehydes.

Table 3.03: Attempted debenzylation of compound **156** using DDQ.

Entry	Conditions	Result
1	DDQ (10 eq.), CH ₂ Cl ₂ , 58 °C, 1 hr	decomposition
2	DDQ (1 eq.), CH ₂ Cl ₂ , 25 °C, 15 hrs	complex mixture

3.6 PMB protecting group strategy

Since the benzyl group was difficult to remove, an alternate protecting group was explored. One group that could be used is a *p*-methoxybenzyl group (PMB). The methoxy functional group would improve the stability of the benzyl cation formed during cleavage of the ether. This would make the PMB group easier to remove using the oxidative conditions described in Table 3.03. In addition to changing the protecting group, the hydroxyacid portion of benzo-resolvin E1 (red) would be installed before the enyne chain (purple). This would avoid forming the benzodiene and enyne units at an early stage in the synthesis, which could be unstable towards the conditions used to deprotect the PMB group (Figure 3.02).

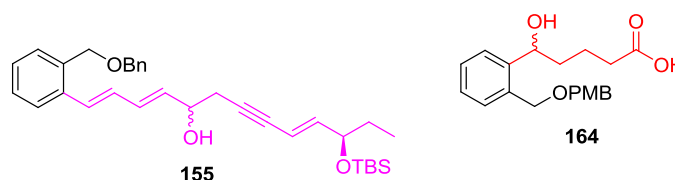
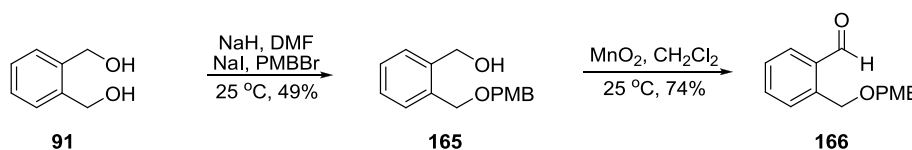


Figure 3.02: Compound **155** and the new target compound **164**.

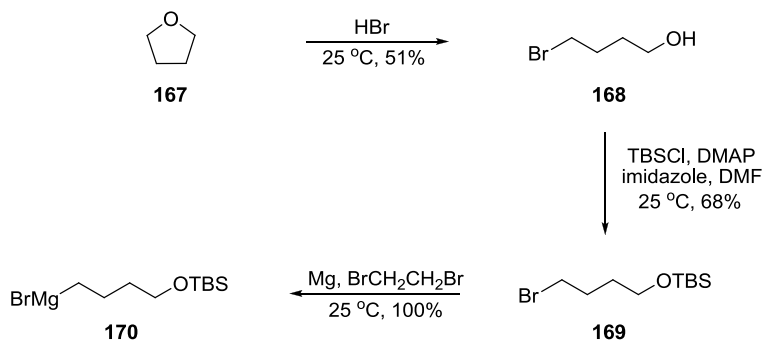
To introduce the PMB group onto the benzyl alcohol, compound **91** in anhydrous dimethylformamide was treated with NaH, followed by the addition of NaI and *p*-methoxybenzyl bromide at room temperature (Scheme 3.23).²³⁵ This afforded compound **165** in 49% yield. The benzyl alcohol was then oxidised using activated manganese dioxide to give the aldehyde **166** in 74% yield.



Scheme 3.23: Preparation of the aldehyde **166**.

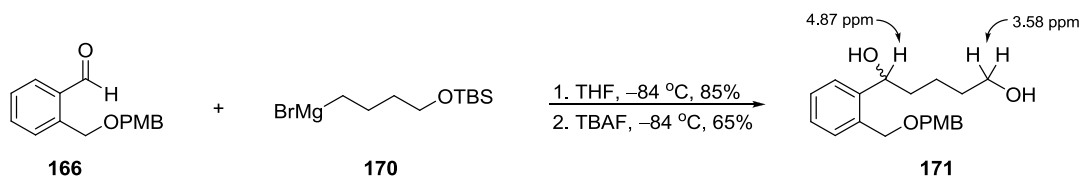
With the aldehyde **166** in hand, focus was shifted towards installing the hydroxyacid portion of the target compound via a Grignard reaction. Due to the instability of the Grignard **82** prepared in Scheme 2.08, the simpler Grignard reagent **170** was synthesised. An acid-catalysed cleavage of tetrahydrofuran, followed by silyl group protection of the primary alcohol and Grignard initiation afforded **170** in 35% yield

in 3 steps (Scheme 3.24).²³⁶⁻²³⁷ Unlike compound **82** (Scheme 2.08), the Grignard reagent **170** is not prone to thermal decomposition.



Scheme 3.24: Preparation of the Grignard reagent **170**.²³⁶⁻²³⁷

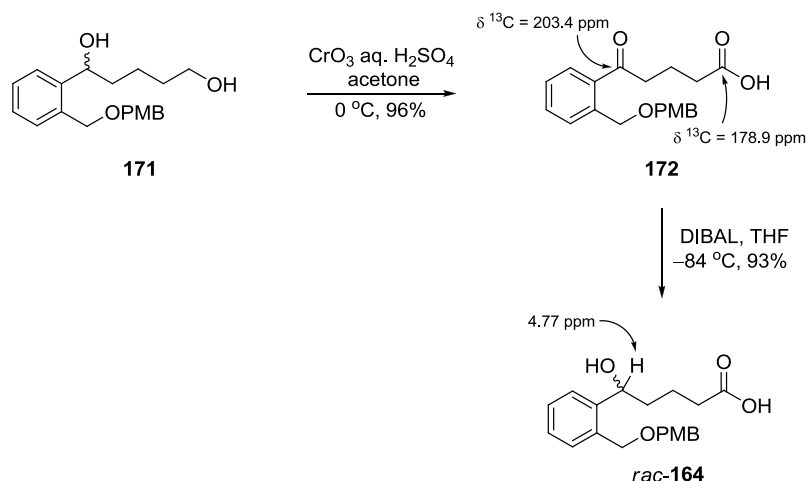
The Grignard reagent **170** was then added to the aldehyde **166** in anhydrous tetrahydrofuran at $-84\text{ }^{\circ}\text{C}$ (Scheme 3.25). This gave the silyl protected product in 85% yield. Without further purification, the crude mixture was treated with TBAF at $-84\text{ }^{\circ}\text{C}$ to furnish the diol **171** in 65% yield (Scheme 3.25). The ^1H NMR spectrum of the product showed a doublet of doublets at 4.87 ppm and a triplet at 3.58 ppm that could be ascribed to the methine and methylene hydrogens of the carbons bearing the hydroxyl groups.



Scheme 3.25: Addition of the Grignard reagent **170** to compound **166**.

The primary and secondary alcohols were then oxidised using Jones reagent to afford the ketoacid **172** in 96% yield (Scheme 3.26). The ^1H NMR spectrum of the crude reaction mixture after four and a half hours showed the disappearance of the signals at 4.87 and 3.58 ppm and the appearance of two resonances at 203.4 and 178.9 ppm in the ^{13}C NMR spectrum. These were assigned to the carbonyl carbon of the ketone and the carboxylic acid respectively. The ketone was then reduced to an alcohol using two equivalents of DIBAL at $-84\text{ }^{\circ}\text{C}$ to give *rac*-**164** in 93% yield. The ^{13}C NMR and ^1H NMR spectra showed the disappearance of a carbonyl resonance at 203.4 ppm and the appearance of a multiplet at 4.77 ppm that was ascribed to the

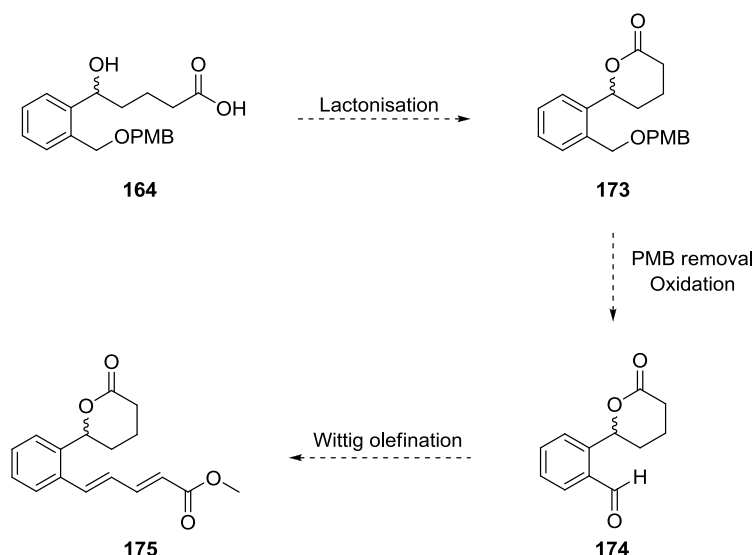
newly formed benzylic hydrogen. The IR spectrum of the product also gave two absorbances at 3390 and 1681 cm^{-1} that were assigned to the alcohol and the carboxylic acid.



Scheme 3.26: Synthesis of *rac*-**164**.

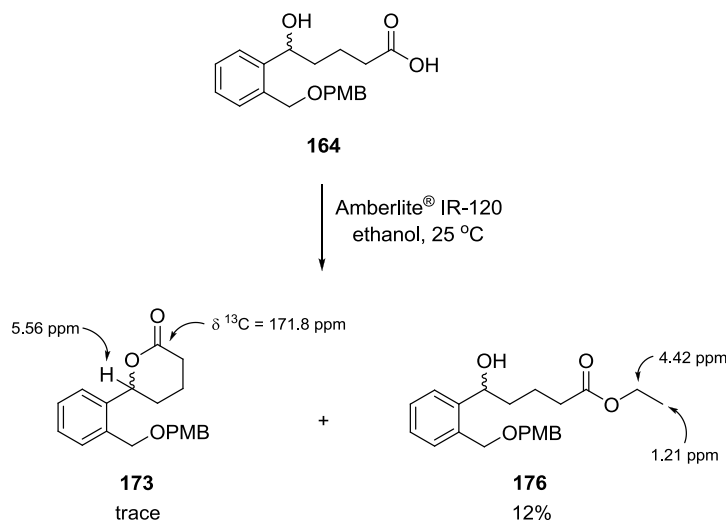
3.7 Lactonisation strategy

Having prepared the hydroxyacid **164**, a suitable synthesis for the lactone **175** was explored. Converting the hydroxyacid to a lactone could be advantageous. It would allow the PMB protected alcohol to be deprotected and oxidised to form compound **174** without the need for an alcohol or a carboxylic acid protecting group (Scheme 3.27). Compound **174** could undergo a Wittig olefination with the ylide of the phosphonium salt **88** to afford the ester **175**. The enyne portion of benzo-resolvin E1 could then be installed in the subsequent steps.



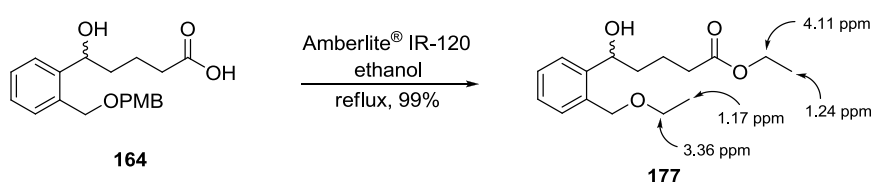
Scheme 3.27: Proposed synthesis of compound **175**.

The lactone **173** could be synthesised using an acidic resin such as Amberlite® IR-120. Thus, compound **164** in ethanol was stirred with catalytic amounts of Amberlite® IR-120 and 3Å molecular sieves at room temperature for 5 hours (Scheme 3.28). Purification of the crude reaction mixture by column chromatography afforded the starting material in 85% yield along with a product assigned as ethyl ester **176** in 12% yield. The ^1H NMR spectrum of compound **176** was similar to the starting material, apart from the appearance of two new resonances at 4.42 and 1.21 ppm that were ascribed to the methylene and methyl hydrogens of the ethyl ester. The ^1H NMR and ^{13}C NMR spectra of the crude reaction mixture also showed trace amounts of a compound that was tentatively assigned as the lactone **173** (Scheme 3.28). The ^1H NMR spectrum showed a doublet of doublets at 5.56 ppm while a resonance at 171.8 ppm was observed in the ^{13}C NMR spectrum. These are in the region expected for the methine hydrogen and the carbonyl carbon of a lactone.



Scheme 3.28: Attempted acid-catalysed lactonisation of compound **164**.

In an attempt to increase the yield of compound **173**, the reaction mixture was heated under reflux for 5 hours (Scheme 3.29). Interestingly the lactone was not observed after this time. Instead a product assigned as compound **177** was afforded in 99% yield.

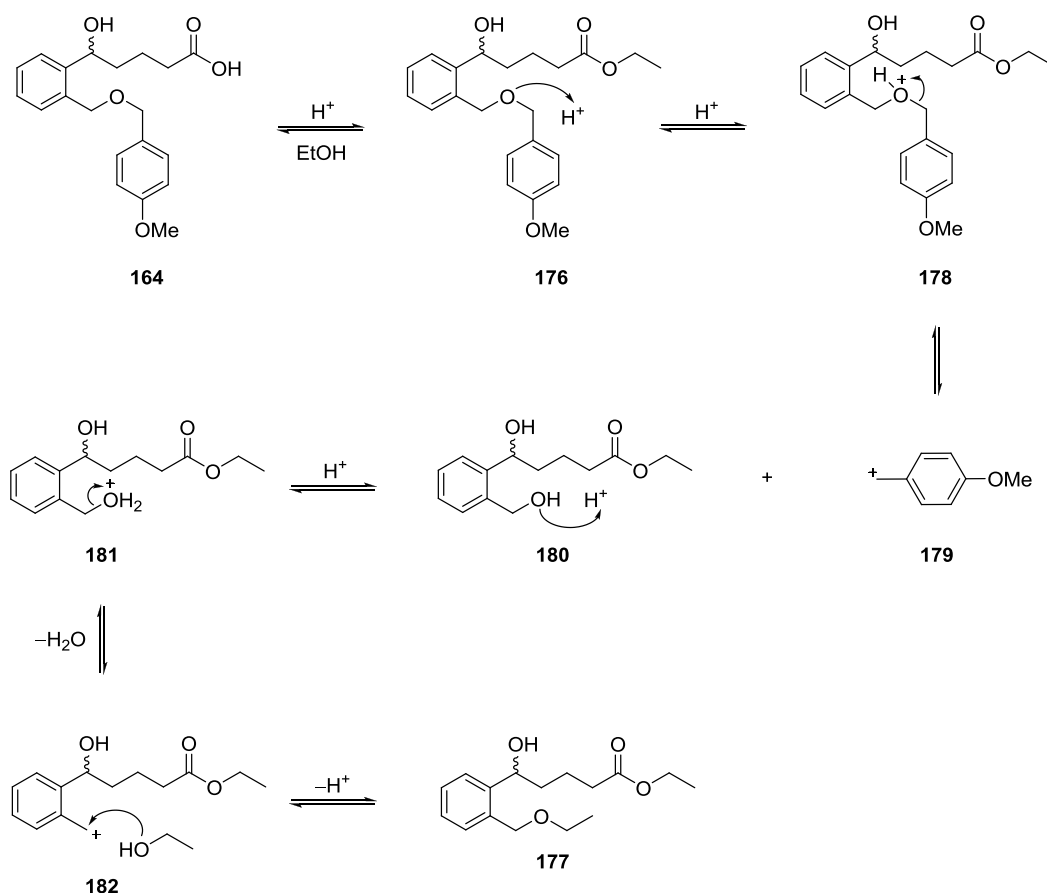


Scheme 3.29: Synthesis of compound **177**.

The ^1H NMR spectrum of the product showed only four aromatic signals between 7.28–7.38 ppm while the signals attributed to the PMB group at 3.77, 4.43 and 4.48 ppm had disappeared. This suggests that the PMB group was removed. The appearance of a quartet at 4.11 ppm and a triplet at 1.24 ppm suggest the formation of an ethyl ester which would support the structure of **177** (Scheme 3.29). Two additional signals at 3.36 (2 H) and 1.17 (3 H) were assigned to the methylene and methyl hydrogens of an ethyl ether (Scheme 3.29). Formation of the two ethyl groups was supported by the ^{13}C NMR spectrum which showed two new methyl carbons at 15.5 and 14.4 ppm.

It was postulated that compound **177** was synthesised by the mechanism shown in Scheme 3.30. An acid-catalysed esterification of the carboxylic acid could give

compound **176**. This compound could be protonated to give the intermediate **178**. Cleavage of the ether by an S_N1 substitution could then afford compound **180** along with the resonance stabilised *p*-methoxybenzylic carbocation **179**. Protonation of the primary benzyl alcohol followed by a second S_N1 or S_N2 substitution with ethanol would give compound **177**.



Scheme 3.30: Proposed mechanism for the synthesis of compound **177**.

Based on the ^1H NMR and ^{13}C NMR spectra of compound **177**, the primary benzyl alcohol is eliminated instead of the secondary benzyl alcohol. A 3D molecular model of the intermediate **180** shows the secondary alcohol to be more sterically hindered than the primary alcohol (Figure 3.03). This is due to the bulky hydroxyacid chain. This could explain why the addition of ethanol takes place at the least hindered primary alcohol.

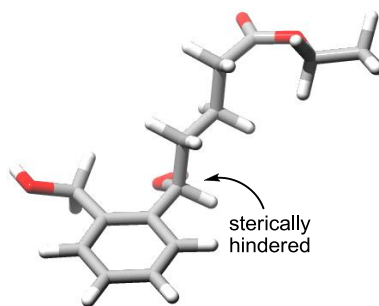
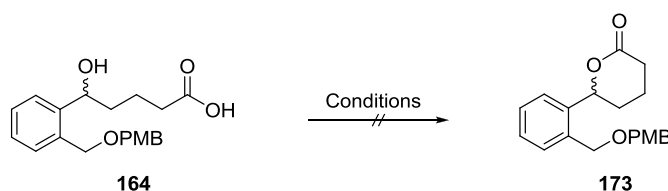


Figure 3.03: A 3D molecular representation of compound **180**.

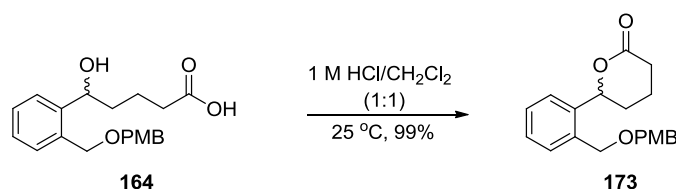
A weaker acid such as trifluoroacetic acid was then tested. To a solution of compound **164** in anhydrous dichloromethane was added one equivalent of trifluoroacetic acid (Table 3.04, entry 1). After stirring the reaction mixture for 12 hours at room temperature, the reaction mixture turned black. The ^1H NMR spectrum of the crude mixture showed complete decomposition of compound **164**. No signals were observed in the aromatic region, suggesting that the PMB ether was readily cleaved under these conditions. Repeating the reaction at 0 °C also gave the same result (Table 3.04, entry 2).

Table 3.04: Treatment of compound **164** with trifluoroacetic acid.



Entry	Conditions	Result
1	Trifluoroacetic acid (1 eq.), CH_2Cl_2 , 25 °C, 12 hrs	decomposition
2	Trifluoroacetic acid (1 eq.), CH_2Cl_2 , 0 °C, 4 hrs	decomposition

In light of these findings, a milder source of acid was investigated. It was envisaged that a biphasic 1 M HCl/dichloromethane system would facilitate the lactonisation of **164** without removing the PMB group. Pleasingly, a compound tentatively assigned as the lactone **173** was furnished in 99% yield after treating compound **164** with a 1:1 mixture of 1 M HCl and dichloromethane at room temperature (Scheme 3.31).



Scheme 3.31: Biphaseic acid mediated lactonisation of compound **164**.

The ^1H NMR spectrum of the crude mixture showed a doublet of doublets at 5.56 ppm that was assigned to the methine hydrogen of the lactone (Figure 3.04). Two signals at 7.29 and 6.90 ppm were also observed in the ^1H NMR spectrum along with a resonance at 3.81 ppm. These signals were ascribed to the aromatic hydrogens and the methoxy hydrogens of the PMB group, suggesting the ether was not cleaved under these conditions. The ^{13}C NMR spectrum of the product showed a shift in the carbonyl resonance from 180.1 to 171.8 ppm. The formation of the lactone was also confirmed by the presence of an absorbance at 1731 cm^{-1} and the absence of the alcohol peak at 3390 cm^{-1} .

Interestingly, starting material was observed in the ^1H NMR spectrum of the crude reaction mixture when it was allowed to stand in a solution of CDCl_3 at room temperature. This was supported by the appearance of the signal at 4.77 ppm that was identical to the methine hydrogen of compound **164** (Figure 3.04). Under these conditions, the lactone **173** hydrolyses to compound **164**. Figure 3.04 shows the ^1H NMR spectrum of the reaction mixture, with equilibrium between the two compounds reached after 2 hours. After this time, the mixture exists as a 1:0.54 ratio of the lactone **173** and compound **164**.

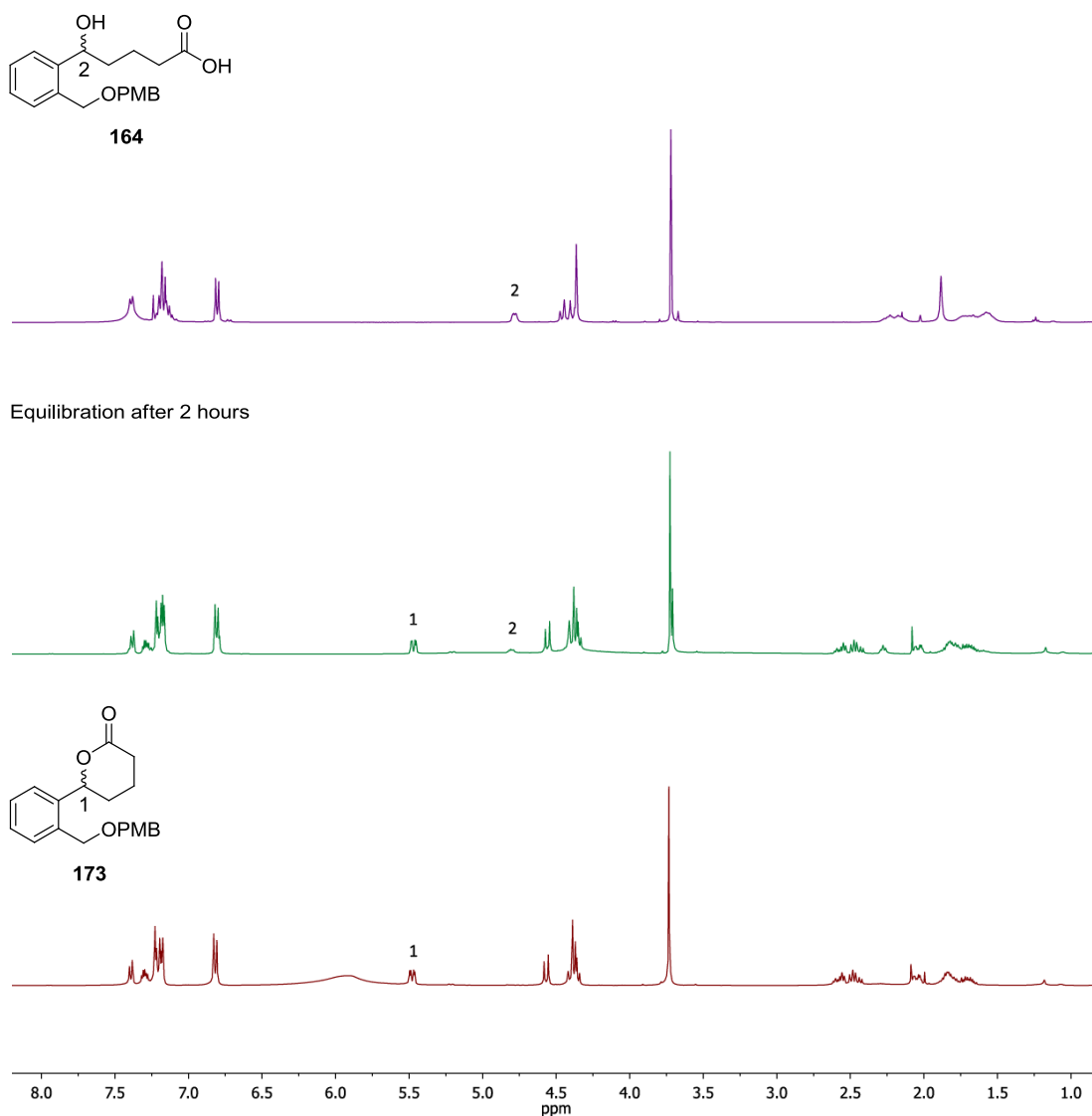


Figure 3.04: Equilibration of the lactone **173** and compound **164** in CDCl_3 after 2 hours.

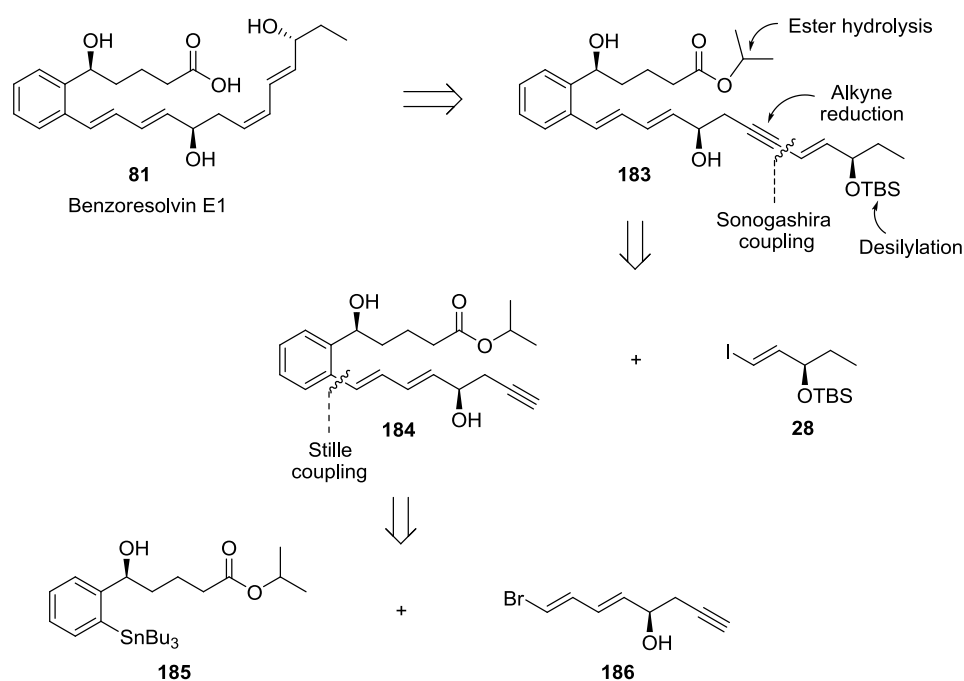
Since the lactone **173** readily equilibrates under standard laboratory conditions, attempts to isolate the product via column chromatography using basic and neutral alumina were unsuccessful. With this in mind, this pathway was abandoned as the lactone was unsuitable for future steps in the synthesis.

Chapter 4

Synthesis of Benzoeresolvin E1: A Cross-Coupling Approach

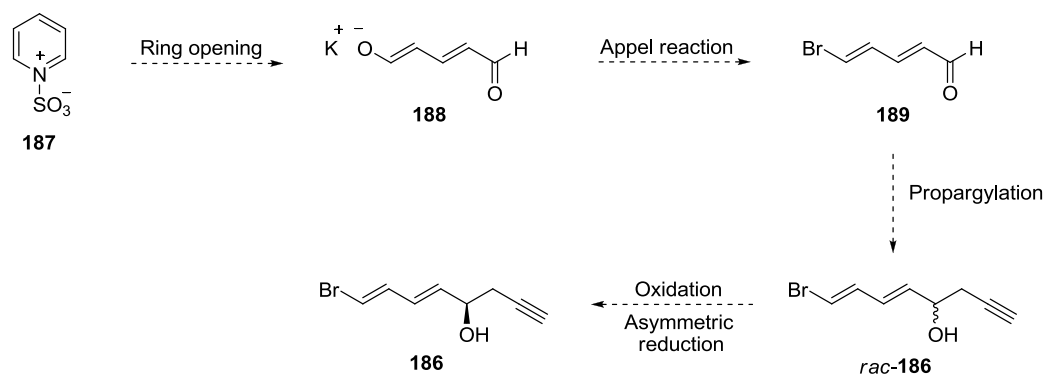
4.1 Revised synthetic pathway

In light of the issues faced in Chapter 3, the synthesis of benzoeresolvin E1 was redesigned. Benzoeresolvin E1 could be prepared from compound **183** in 3 steps (Scheme 4.01). These steps are similar to the final steps in the synthesis of resolvin E1 developed by Allard.¹⁸² They involve the removal of the silyl protecting group, reduction of the alkyne and hydrolysis of the isopropyl ester. Following the same conditions as described in Scheme 3.19, the enyne of the intermediate **183** could be synthesised by a Sonogashira reaction between the alkyne **184** and the iodide **28**. The key reaction in the proposed synthesis is the Stille coupling between the stannane **185** and the bromide **186** to give the alkyne **184**. Unlike the proposed synthesis of benzoeresolvin E1 in Chapter 3, this approach would afford the benzodiene portion of the target compound with limited use of protecting groups. Thus, circumventing the problems encountered in the previous chapter.



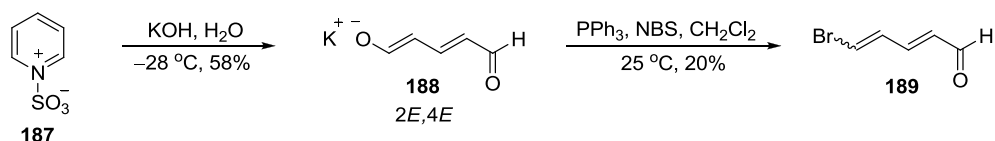
Scheme 4.01: Revised retrosynthesis of benzoeresolvin E1 **81**.

Focusing on the (*R*)-alcohol **186**, this compound could be synthesised from the sulfur trioxide pyridine complex **187** in 5 steps (Scheme 4.02). Following a literature procedure,²³⁸ treatment of **187** with potassium hydroxide would afford the ring opened potassium salt **188**, which could undergo an Appel reaction to give the bromide **189**. Addition of propargylmagnesium bromide to this product could furnish *rac*-**186**. A tandem oxidation-reduction reaction could then give the (*R*)-enantiomer of alcohol **186**.



Scheme 4.02: Planned synthesis of the (*R*)-alcohol **186**.

Following the procedure described by Soulez and co-workers,²³⁸ addition of potassium hydroxide to a freshly prepared sulfur trioxide pyridine complex in water gave the isometrically pure *2E,4E*-diene of **188** in 58% yield (Scheme 4.03).²³⁹ Compound **188** was then treated with *N*-bromosuccinimide and triphenylphosphine to afford the bromide **189** in 20% yield as a 3:2 mixture of *2E,4E* and *2E,4Z* stereoisomers. This was lower than the 72% yield reported by Soulez.²³⁸



Scheme 4.03: Synthesis of the bromide **189**.

The aldehyde and vinylic hydrogens of the two isomers were assigned by comparing the ¹H NMR spectrum of the product with the literature spectrum.²³⁸ These are shown in Figure 4.01.

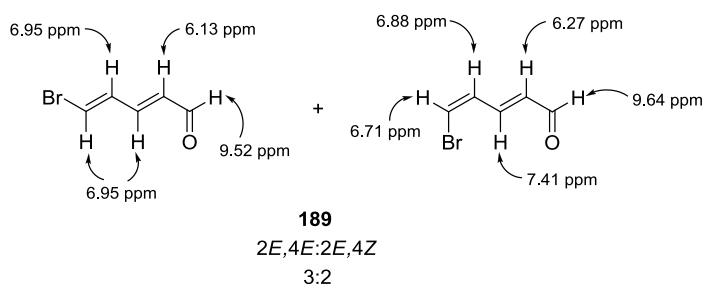
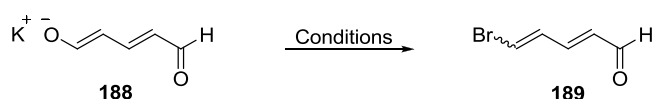


Figure 4.01: Proton assignment for the isomers of **189**.

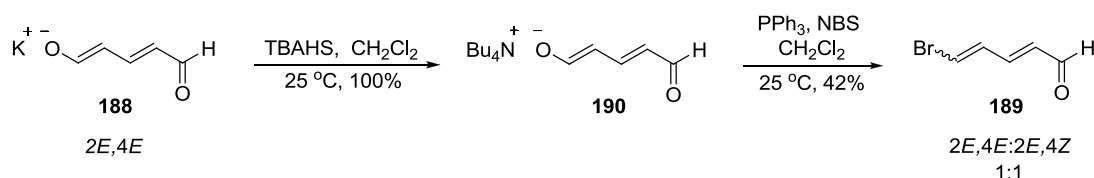
Attempts were made to improve the yield of compound **189** by increasing the reaction time, using freshly recrystallised *N*-bromosuccinimide and changing the bromine source (Table 4.01). Disappointingly, the yield remained low under these conditions. This could be attributed to the poor solubility of the starting material **188** in dichloromethane.

Table 4.01: Conditions trialled to improve the yield of compound **189**.



Entry	Conditions	Result
1	PPh ₃ , NBS, CH ₂ Cl ₂ , 25 °C, 9 hrs	20%
2	PPh ₃ , NBS, CH ₂ Cl ₂ , 25 °C, 24 hrs	21%
3	PPh ₃ , recrystallised NBS, CH ₂ Cl ₂ , 25 °C, 24 hrs	21%
4	PPh ₃ , Br ₂ , CH ₂ Cl ₂ , 25 °C, 24 hrs	18%

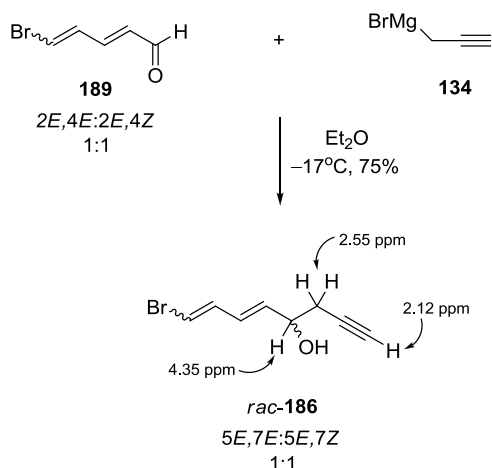
A tetrabutylammonium salt of alkoxide **188** was also prepared. The lipophilic counterion would increase the solubility of the starting material in dichloromethane, thus improving the yield of compound **189**. To prepare the tetrabutylammonium salt, the potassium salt **188** was treated with tetrabutylammonium hydrogen sulfate at room temperature (Scheme 4.04).²³⁹ This gave compound **190** in quantitative yields. When compound **190** was subjected to the same conditions in Scheme 4.03, the bromide **189** was afforded in 42% yield as a 1:1 mixture of isomers.



Scheme 4.04: Preparation of the bromide **189** from the tetrabutylammonium salt **190**.

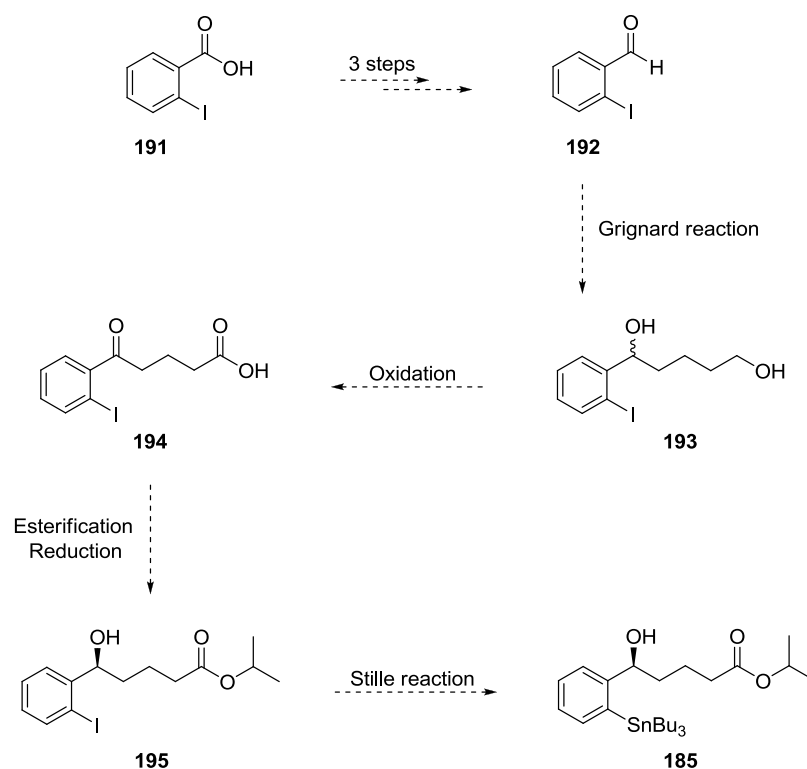
As there is a 1:1 mixture of stereoisomers, an isomerisation was attempted to equilibrate the mixture to the more thermodynamically stable 2E,4E-product. Following the procedure by Wang and co-workers,²⁴⁰ the bromide **189** was treated with a catalytic amount of iodine in anhydrous dichloromethane and stirred at room temperature for 8 hours. The ¹H NMR spectrum of an aliquot taken after 3 hours showed an enrichment of the desired 2E,4E-isomer (71%). After prolonging the reaction time to 8 hours, the quantity of the 2E,4E-isomer was only marginally improved (76%), suggesting that equilibrium had been reached. This was consistent with the results obtained by Wang and co-workers.²⁴⁰ Attempts to separate the isomers by column chromatography or recrystallisation were unsuccessful.²⁴⁰ In view of this, the isomerisation was postponed until the subsequent step.

To prepare the alcohol **186**, compound **189** was treated with a 1 M solution of propargylmagnesium bromide in anhydrous ether at −17 °C. This gave *rac*-**186** in 75% yield as a 1:1 mixture of the stereoisomers (Scheme 4.05). The addition of the propargyl portion was supported by the ¹H NMR spectrum, with the appearance of signals at 4.35, 2.55 and 2.12 ppm indicative of the methine, methylene and acetylenic hydrogens respectively. The disappearance of the carbonyl signal in the ¹³C NMR spectrum of the crude mixture suggested complete consumption of compound **189** while the absence of a signal around the 200–210 ppm region confirmed the alkyne had not rearranged to an allene.



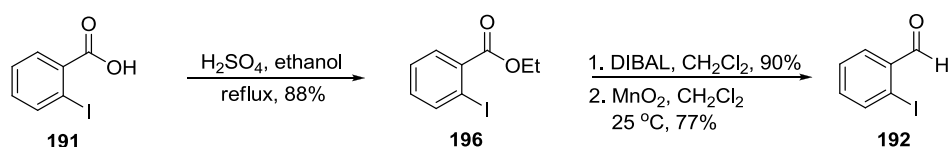
Scheme 4.05: Addition of propargylmagnesium bromide to the aldehyde **189**.

Having prepared *rac*-**186**, the synthesis of compound **185** was attempted. The tandem oxidation-reduction reaction for the planned synthesis of the (*R*)-alcohol **186** was postponed to see if the proposed synthesis of the stannane **185** would work. To prepare **185**, *o*-iodobenzoic acid **191** was used as the starting material (Scheme 4.06). This compound can be converted into *o*-iodobenzaldehyde **192** in 3 steps.²⁴¹ The addition of the Grignard reagent **170** to *o*-iodobenzaldehyde could afford the diol **193**, with the product oxidised to the ketoacid **194** using Jones reagent. The carboxylic acid of **194** could be esterified with isopropyl alcohol and the ketone reduced to give the (*S*)-alcohol of **195**. The final step in the planned synthesis is a Stille reaction between the iodide **195** and hexabutyldistannane to afford the stannane **185**.



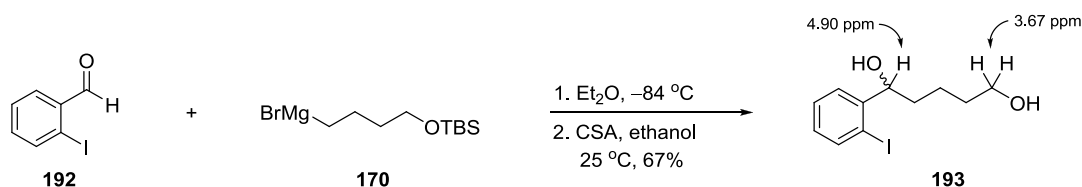
Scheme 4.06: Proposed synthesis of the stannane **185**.

Starting from *o*-iodobenzoic acid, the carboxylic acid was esterified with ethanol to afford compound **196** in 88% yield (Scheme 4.07). The ethyl ester of **196** was then reduced to an alcohol using DIBAL. Subsequent oxidation of the alcohol using activated manganese dioxide gave *o*-iodobenzaldehyde **192**.²⁴¹



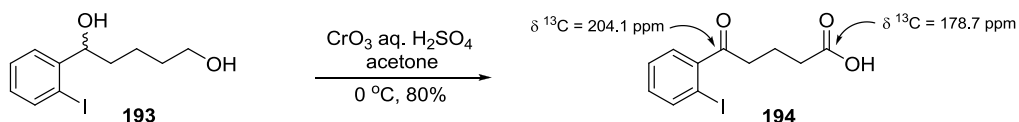
Scheme 4.07: Preparation of *o*-iodobenzaldehyde **192**.

o-Iodobenzaldehyde was then treated with the Grignard reagent **170** in anhydrous ether at -84°C followed by removal of the silyl group with CSA to afford the diol **193** in 67% yield over 2 steps (Scheme 4.08). The ^1H NMR spectrum of the product showed a doublet of doublets at 4.90 ppm and a triplet at 3.67 ppm. These were ascribed to the methine and methylene hydrogens of the hydroxyl bearing carbons respectively. The IR spectrum also showed two absorbances at 3291 and 3197 cm^{-1} that were assigned to the two hydroxyl groups.



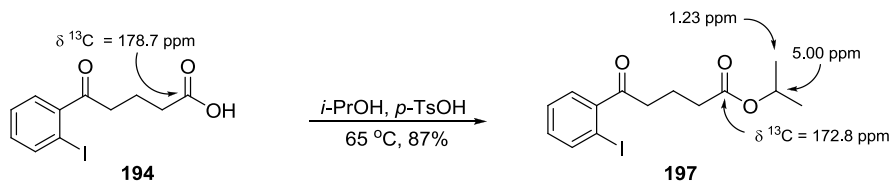
Scheme 4.08: Addition of the Grignard reagent **170** to *o*-iodobenzaldehyde **192**.

The benzylic alcohol and primary alcohol of compound **193** were oxidised using Jones reagent to furnish the ketoacid **194** in 80% yield (Scheme 4.09). The product showed two new resonances at 204.1 and 178.7 ppm in the ^{13}C NMR spectrum. These were ascribed to the newly formed ketone and carboxylic acid. The IR spectrum also showed two absorbances at 1702 and 1688 cm^{-1} that were consistent with the absorbances expected for the ketone and carboxylic acid.



Scheme 4.09: Preparation of the ketoacid **194**.

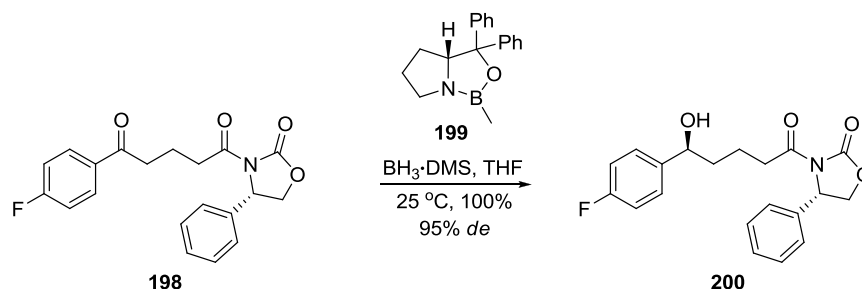
Adapting the procedure by Allard and co-workers,¹⁸² compound **194** was esterified with isopropyl alcohol and *p*-toluenesulfonic acid to afford the ketoester **197** (Scheme 4.10). The ^1H NMR spectrum of the product showed a methine resonance at 5.00 ppm and a methyl peak at 1.23 ppm that were attributed to the isopropyl ester. The ^{13}C NMR spectrum also gave a new signal at 172.8 ppm that was assigned to the carbonyl carbon of the ester. This was upfield compared to the carboxylic acid resonance at 178.7 ppm.



Scheme 4.10: Synthesis of the ketoester **197**.

With the ketoester **197** in hand, attention was focused on the synthesis of the (*S*)-alcohol **195**. This compound could be prepared using (*R*)-CBS catalyst and $\text{BH}_3\cdot\text{DMS}$. An example of this reaction in the literature is shown in Scheme 4.11.

Using these reagents, Fu and co-workers selectively reduced compound **198**, giving the (*S*)-alcohol **200** in 100% yield and 95% *de*.²⁴²



Scheme 4.11: A literature example of the asymmetric reduction of the ketone **198**.²⁴²

The striking similarity between the ketoester **197** and the keto-amide **198** suggest the (*S*)-alcohol **195** could be synthesised enantioselectively using these conditions. The proposed transition states for the CBS reduction are shown in Figure 4.02. The six membered transition state **202** is not favourable as the bulky aryl iodide in the pseudoaxial position clashes with the methyl substituent of the CBS catalyst. The transition state **201** however is less hindered and allows the hydride transfer to take place from the upper face of the ketone, thus giving the (*S*)-enantiomer.

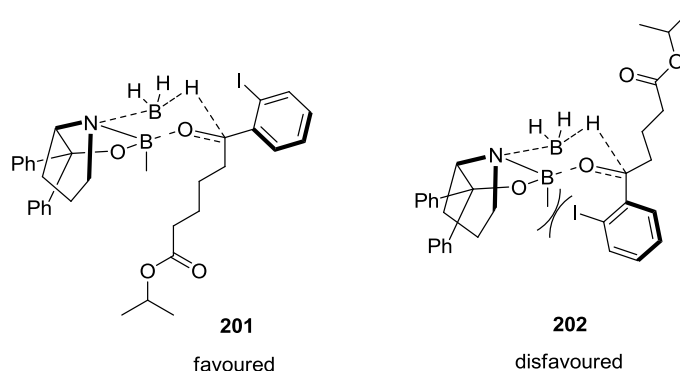
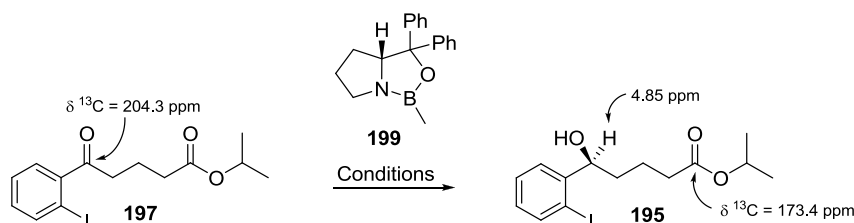


Figure 4.02: Proposed transition states for the reduction of the ketoester **197**.

Following the same conditions outlined by Fu,²⁴² dropwise addition of 0.6 equivalents of $\text{BH}_3 \cdot \text{DMS}$ to a solution of (*R*)-CBS (8 mol%) catalyst and the ketoester **197** in anhydrous tetrahydrofuran at 25 °C gave the alcohol **195** in 70% yield and 60% *ee* (Table 4.02, entry 1). Formation of the alcohol was confirmed by an increase in the *m/z* ratio by two units along with the appearance of a doublet of doublets at 4.85 ppm in the ^1H NMR spectrum. The presence of the ester peak at 173.4 ppm and the absence of the ketone resonance at 204.3 ppm in the ^{13}C NMR

spectrum suggested that the reduction was chemoselective. Repeating the reaction at 0 °C and –84 °C improved the selectivity, giving compound **195** in 87% and 94% *ee* respectively (Table 4.02, entries 2 and 3).

Table 4.02: Asymmetric reduction of compound **197** at varying temperatures.



Entry	Conditions	Yield	<i>ee</i> *
1	BH ₃ •DMS (0.6 eq.), (<i>R</i>)-CBS (8 mol%), THF, 25 °C, 3 hrs	70%	60%
2	BH ₃ •DMS (0.6 eq.), (<i>R</i>)-CBS (8 mol%), THF, 0 °C, 5 hrs	71%	87%
3	BH ₃ •DMS (0.6 eq.), (<i>R</i>)-CBS (8 mol%), THF, –84 °C, 8 hrs	70%	94%

* Based on chiral HPLC.

4.2 Racemisation of the alcohol **195**

In order to confirm the absolute stereochemical configuration of the alcohol **195**, a crystal structure was required. Disappointingly, crystals for the oily residues of the alcohol **195** and its *p*-bromobenzoate derivative could not be attained with solvents such as ethanol, diethyl ether, petroleum spirits, chloroform and dichloromethane. In view of this, compound **195** was reduced to the enantiomerically pure diol **193** using DIBAL. Compound **193** was optically active, suggesting that racemisation had not occurred during the reduction. This compound was also a solid at room temperature, making it easier to grow crystals. Using chloroform as the solvent, crystals of compound **193** were obtained and the X-ray structure was determined by Brian Skelton at UWA. Unfortunately the crystals were spirocentric, suggesting **193** had racemised in solution. This finding prompted the investigation of the racemisation of compound **195** by monitoring the optical rotation (Figure 4.03). When left to stand in chloroform at room temperature, the enantiomerically pure alcohol of **195** completely racemised over 10 days ($T_{1/2}$ = 4 days). The same outcome was observed when **195** was left to stand in chloroform in the presence of 5 mol% of triethylamine due to the generation of the acidic ammonium species (Figure 4.03).

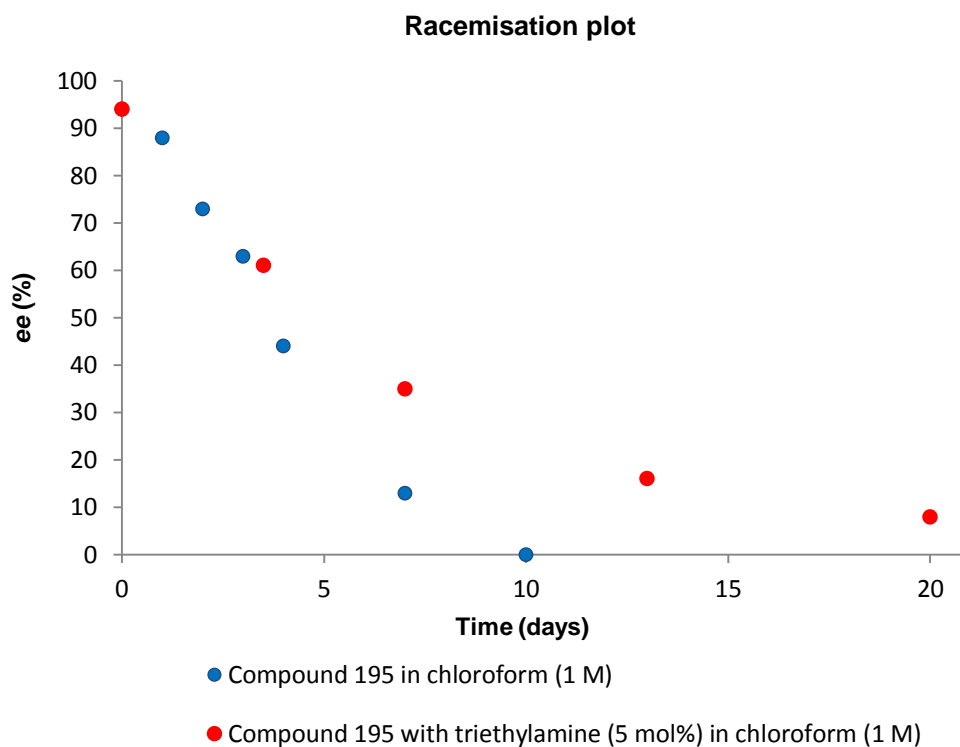
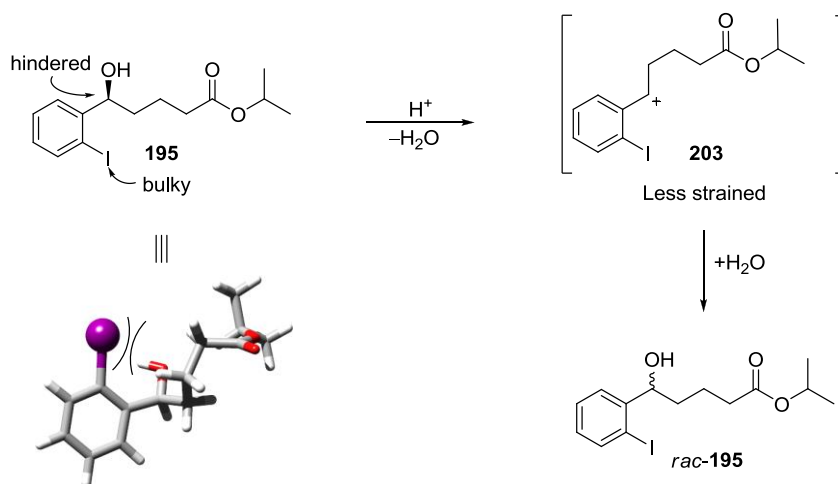


Figure 4.03: Racemisation plot of compound **195** at 24 °C.

To date, this is the first reported example of the racemisation of a benzylic alcohol with an *ortho* substituted aryl iodide. The racemisation of the alcohol in compound **195** was rationalised by the steric effects provided by the bulky iodo group (Scheme 4.12). To relieve the steric strain at this position, the alcohol could eliminate to give the sp^2 hybridised carbocation **203**. Based on the racemisation study in Figure 4.03, this is promoted with acid produced from the chloroform. The carbocation **203** is less strained than the (*S*)-alcohol **195**, thus acting as the driving force for racemisation at this position. Subsequent addition of a water molecule could reform the alcohol **195** as a racemate.



Scheme 4.12: Proposed pathway for the racemisation of compound **195**.

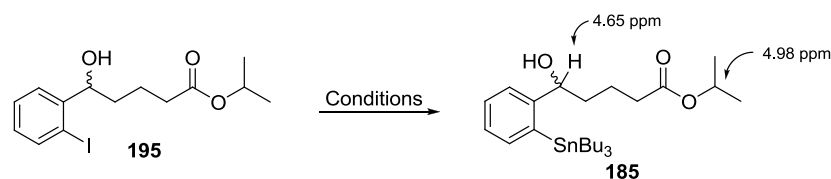
4.3 Stille coupling reaction

Having established that the enantiomerically pure alcohol of **195** racemises under normal laboratory conditions, *rac*-**195** was used in the remaining steps. Subsequently, focus was shifted towards the preparation of the stannane **185**. This compound could be synthesised via a Stille reaction between *rac*-**195** and hexabutyldistannane. Initial attempts to form the stannane **185** by heating *rac*-**195** and hexabutyldistannane with Pd(PPh₃)₄ in anhydrous toluene using the procedure described by Azizian and co-workers were unsuccessful.²⁴³ This led to quantitative recovery of starting material (Table 4.03, entries 1 and 2).

Polar solvents such as tetrahydrofuran, dioxane and dimethylformamide have been shown to increase the rate of the transmetallation step and thus improve the rate of the Stille reaction.²⁴⁴⁻²⁴⁵ This is achieved by enhancing the nucleophilicity of the distannane reagent through a stable solvent-tin complex.²⁴⁴⁻²⁴⁵ Accordingly, the reaction was repeated using tetrahydrofuran as the solvent. After stirring the mixture for 12 hours at 60 °C, a new spot was observed by TLC (Table 4.03, entry 3). The appearance of a small resonance at 4.65 ppm in the ¹H NMR spectrum of the crude reaction mixture could be ascribed to the benzylic hydrogen of **185**. This signal is upfield compared to the same hydrogen of *rac*-**195**. This is consistent with the deshielding effect of the iodo functionality on that carbon, which is greater than the stannane group. The appearance of a cluster of aromatic signals between 6.80–7.80 ppm and a signal at 4.98 ppm that could be attributed to the methine

hydrogen of the isopropyl ester, add further evidence to support the formation of the stannane **185**. Disappointingly, only a trace amount of **185** was observed when the reaction was stirred for a longer period of time (Table 4.03, entry 4). Changing the solvent to anhydrous dioxane and subjecting the reaction mixture to elevated temperatures gave the same outcome (Table 4.03, entries 5 and 6).

Table 4.03: Attempted Stille coupling of compound **195**.



Entry	Conditions	Result
1	Sn ₂ Bu ₆ (1.2 eq.), Pd(PPh ₃) ₄ (7 mol%), toluene, 60 °C, 12 hrs	no reaction
2	Sn ₂ Bu ₆ (1.2 eq.), Pd(PPh ₃) ₄ (7 mol%), toluene, 100 °C, 48 hrs	no reaction
3	Sn ₂ Bu ₆ (1.2 eq.), Pd(PPh ₃) ₄ (7 mol%), THF, 60 °C, 12 hrs	trace
4	Sn ₂ Bu ₆ (1.2 eq.), Pd(PPh ₃) ₄ (7 mol%), THF, 60 °C, 48 hrs	trace
5	Sn ₂ Bu ₆ (1.2 eq.), Pd(PPh ₃) ₄ (7 mol%), dioxane, 100 °C, 12 hrs	trace
6	Sn ₂ Bu ₆ (1.2 eq.), Pd(PPh ₃) ₄ (7 mol%), dioxane, 100 °C, 48 hrs	trace

To rationalise the poor reactivity of *rac*-**195**, a closer examination of the mechanism for the Stille reaction was required (Figure 4.04). The first step in the reaction is the oxidative addition of the palladium(0) catalyst across the aryl-iodide bond of compound **195** to give **204**. This step is favourable for electron poor aromatic compounds such as the ketoester **197**. Compound **195** however is an electron rich aromatic compound. This is owing to the *ortho* substituted benzyl alcohol. Compared to an electron poor aromatic system, more forcing conditions are required for the aryl-iodide bond to dissociate upon palladium(0) insertion, making it a poor substrate for the Stille reaction. Compound **195** is also sterically hindered due to the bulky *ortho* substituted hydroxyester chain. This makes **195** sluggish towards cross-coupling. To circumvent this problem, different palladium catalysts and additives could be tested to accelerate the Stille reaction.²⁴³⁻²⁴⁶ These will be investigated in subsequent steps.

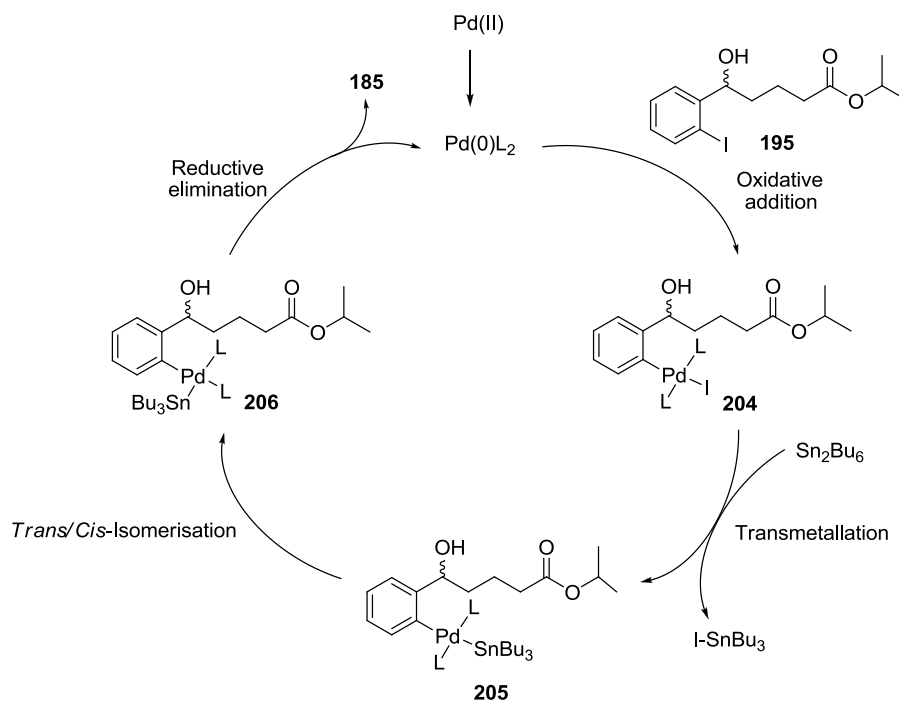
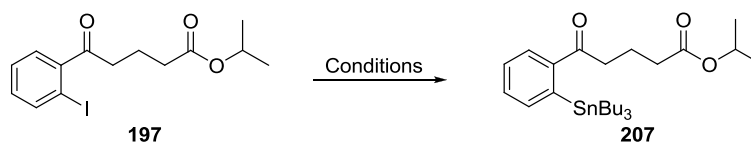


Figure 4.04: Stille coupling mechanism for the stannane **185**.

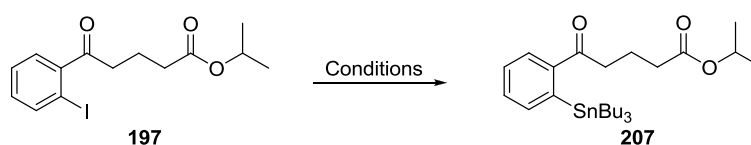
In view of the poor reactivity of *rac*-**195**, the Stille reaction was repeated with the ketoester **197**. This compound has an electron poor aromatic ring due to the electron withdrawing ketone. This would be favourable for oxidative addition since less energy is required to dissociate the aryl-iodide bond. Pleasingly, heating the ketoester **197** with hexabutyldistannane and $\text{Pd(PPh}_3)_4$ in anhydrous tetrahydrofuran for 12 hours afforded the desired stannane **207** in 16% yield and starting material in 78% yield (Table 4.04, entry 1).

The high resolution mass spectrum showed a molecular ion ($m/z = 525.2407$ [$\text{M}-57 (\text{C}_4\text{H}_9)]^+$) that was consistent with the loss of a butyl group for the stannane **207**. Five new resonances between 0.84–1.49 ppm were observed in the ^1H NMR spectrum of the product. These were assigned to the butyl chain of the stannane. The ^{13}C NMR spectrum also showed two new signals at 201.2 and 172.9 ppm that could be ascribed to the ketone and ester functional groups. In light of this promising result, the reaction mixture was stirred for an additional 12 hours, giving the stannane **207** in 38% yield (Table 4.04, entry 2). The reaction mixture was also dosed twice with $\text{Pd(PPh}_3)_4$ and stirred for 48 hours to afford **207** in 42% yield (Table 4.04, entry 3).

Table 4.04: Preparation of the stannane **207**.

Entry	Conditions	Result
1	Sn ₂ Bu ₆ (1.2 eq.), Pd(PPh ₃) ₄ (7 mol%), THF, 60 °C, 12 hrs	16%
2	Sn ₂ Bu ₆ (1.2 eq.), Pd(PPh ₃) ₄ (7 mol%), THF, 60 °C, 24 hrs	38%
4	Sn ₂ Bu ₆ (1.2 eq.), Pd(PPh ₃) ₄ (2 x 7 mol%), THF, 60 °C, 48 hrs	42%

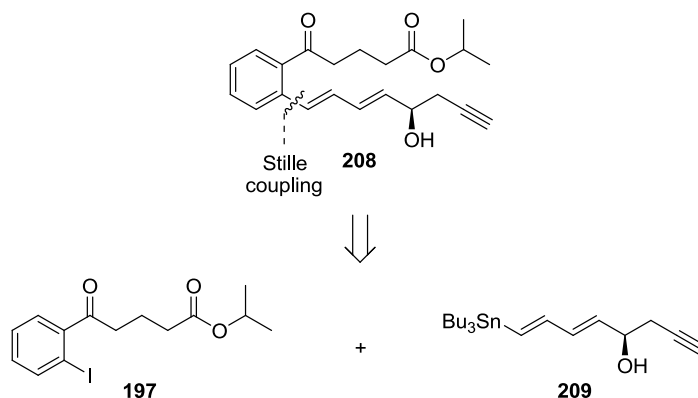
Several precatalysts were also investigated to improve the yield of the stannane **207**. Following the same conditions given in Table 4.04, the reaction was repeated with Pd(PPh₃)₂Cl₂ (Table 4.05, entry 2). The ¹H NMR spectrum of the crude sample showed a complex mixture of compounds, with numerous aromatic signals in the region of 7.30–8.00 ppm. The crude sample appeared to be a mixture of the starting material, the product and several other unidentified compounds. A palladium catalyst with a bidentate ligand was also tested. Catalysts with bidentate ligands such as Pd(dppf)₂Cl₂•DCM are known to have larger bite angles.²⁴⁷⁻²⁵⁰ They can promote the oxidative addition and reductive elimination steps, thus accelerating the Stille reaction.²⁴⁷⁻²⁵⁰ Disappointingly, when the reaction was repeated with Pd(dppf)₂Cl₂•DCM, a complex mixture of products was observed in the ¹H NMR spectrum of the crude mixture (Table 4.05, entry 3).

Table 4.05: Different palladium catalysts tested for the Stille reaction.

Entry	Conditions	Result
1	Sn ₂ Bu ₆ (1.2 eq.), Pd(PPh ₃) ₄ (7 mol%), THF, 60 °C, 48 hrs	207 (42%)
2	Sn ₂ Bu ₆ (1.2 eq.), Pd(PPh ₃) ₂ Cl ₂ (7 mol%), THF, 60 °C, 12 hrs	complex mixture
3	Sn ₂ Bu ₆ (1.2 eq.), Pd(dppf) ₂ Cl ₂ •DCM (7 mol%), THF, 60 °C, 36 hrs	complex mixture

In view of these results, a different stannane was explored. Ideally, the Stille reaction would be repeated using hexamethyldistannane since it is less hindered than the

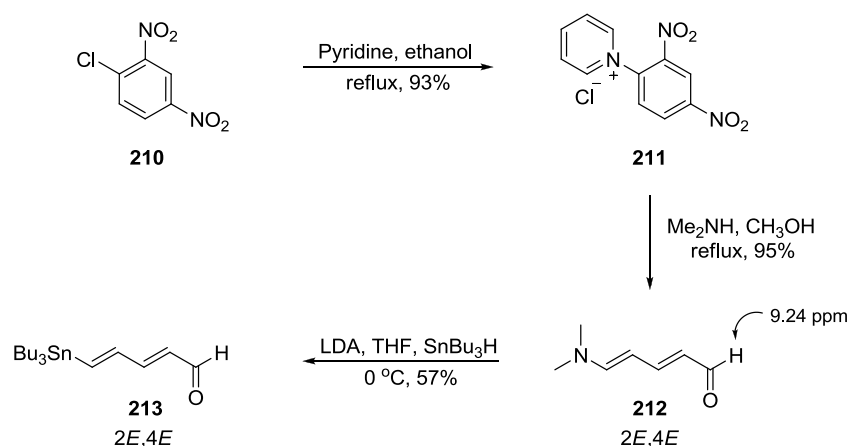
butyl derivative.²⁴⁷⁻²⁴⁸ However, hexamethyldistannane is more toxic and was understandably avoided. An alternate strategy involves swapping coupling partners to give the iodide **197** and the stannane **209**. This approach would circumvent the preparation of the sterically hindered stannane **207** (Scheme 4.13).



Scheme 4.13: Stille reaction with compounds **197** and **209**.

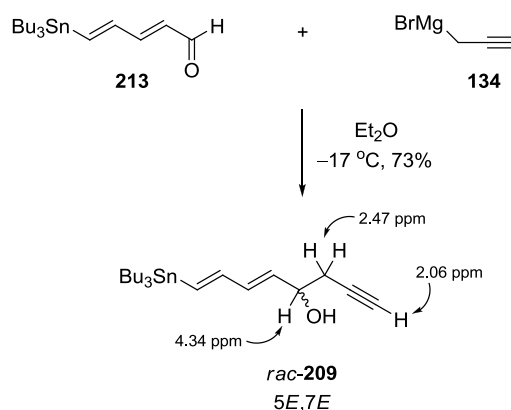
To synthesise compound **209**, the pathway developed by Michels and co-workers in Scheme 4.14 was implemented.²⁵¹ Starting from 2,4-dinitro-1-chlorobenzene **210**, the pyridinium salt **211** was afforded in 93% yield via a Zincke reaction. The reaction can be viewed as the nucleophilic aromatic substitution of 2,4-dinitro-1-chlorobenzene with pyridine. Treatment of **211** with dimethylamine then gave compound **212** in 95% yield. The ¹H NMR spectrum of the product showed four signals between 5.26–7.09 ppm that were assigned to the four vinylic hydrogens while the doublet of doublets at 9.24 ppm was consistent with the chemical shift for the aldehyde hydrogen.²⁵¹

The aldehyde **212** was then converted into the stannane **213** via the addition of lithium tributyltin followed by elimination of lithium dimethylamide. Compound **213** was afforded as the isometrically pure *2E,4E*-isomer in 57% yield. This was higher than the yield reported by Michels (55%).²⁵¹ The ¹H NMR spectrum of the product matched the spectroscopic data reported in the literature,²⁵¹ with the appearance of four new resonances at 1.48–1.53, 1.25–1.37, 0.96 and 0.89 ppm ascribed to the butyl chain of the stannane.



Scheme 4.14: Preparation of the stannane **213**.

To synthesise compound **209**, the same conditions in Scheme 4.05 were used. Accordingly, the aldehyde **213** in anhydrous ether at $-17\text{ }^{\circ}\text{C}$ was treated with propargylmagnesium bromide to give the *5E,7E*-isomer of *rac*-**209** in 73% yield (Scheme 4.15). The appearance of three signals at 4.34, 2.47 and 2.06 ppm in the ^1H NMR spectrum of the product could be attributed to the newly formed methine, methylene and acetylenic hydrogens of the propargyl group. The ^{13}C NMR spectrum also showed two signals at 80.5 and 71.1 ppm that were assigned to the acetylenic carbons and a resonance at 70.5 ppm ascribed to the hydroxyl bearing carbon.



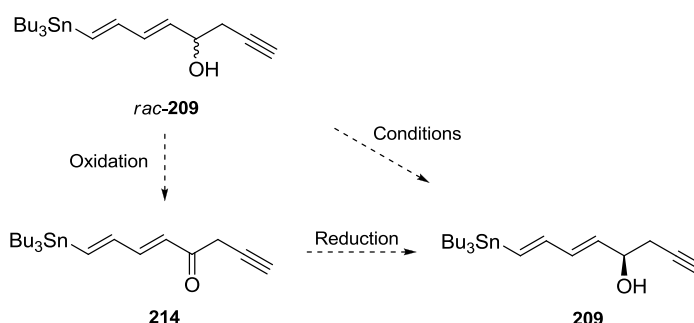
Scheme 4.15: Addition of propargylmagnesium bromide to the aldehyde **213**.

With compound **209** in hand, focus was shifted towards the synthesis of the (*R*)-enantiomer. This could be formed from *rac*-**209** by a sequential oxidation-reduction reaction. Studies have shown that under acidic and basic conditions, propargyl ketone substrates are unstable and can isomerise to allenes.²⁵²⁻²⁵³ With this in mind, a

one pot oxidation and reduction was implemented using mild conditions to avoid isolating the ketone **214**.

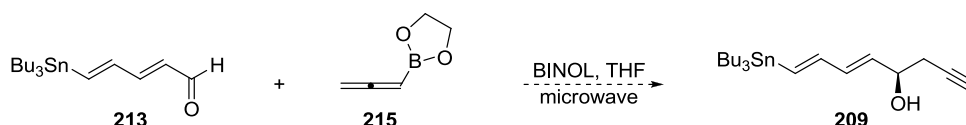
Dess-Martin periodinane was initially tested as the oxidant (Table 4.06, entry 1). Complete consumption of the starting material was noted by TLC after 24 hours. After this time, the reaction mixture was treated with (*R*)-CBS catalyst and BH₃•DMS at –84 °C. The ¹H NMR spectrum of the crude reaction mixture was not promising. Only the butyl signals of the stannane group were evident, with no signals observed in the vinylic or aliphatic region. Trace amounts of acetic acid released from the oxidant could account for this result. The acid could isomerise the propargylic ketone to a propargylic allene. This compound would be highly reactive and lead to degradation. The same outcome occurred when manganese dioxide was investigated as the oxidant, with complete decomposition of the starting material noted in the ¹H NMR spectrum of the crude mixture (Table 4.06, entry 2). Decomposition of the reaction mixture was also observed when milder Swern oxidative conditions were used (Table 4.06, entry 3).

Table 4.06: A one pot oxidation and reduction of *rac*-**209**.



Entry	Conditions	Result
1	1. DMP (1 eq.), CH ₂ Cl ₂ , 25 °C, 24 hrs 2. (<i>R</i>)-CBS (7 mol%), BH ₃ •DMS (0.6 eq.), CH ₂ Cl ₂ , –84 °C, 8 hrs	decomposition
2	1. MnO ₂ (10 eq.), CH ₂ Cl ₂ , 25 °C, 24 hrs 2. (<i>R</i>)-CBS (7 mol%), BH ₃ •DMS (0.6 eq.), CH ₂ Cl ₂ , –84 °C, 8 hrs	decomposition
3	1. Oxalyl chloride (1 eq.), DMSO (1 eq.), NEt ₃ (1 eq.), THF, –84 °C, 5 hrs 2. (<i>R</i>)-CBS (7 mol%), BH ₃ •DMS (0.6 eq.), THF, –84 °C, 8 hrs	decomposition

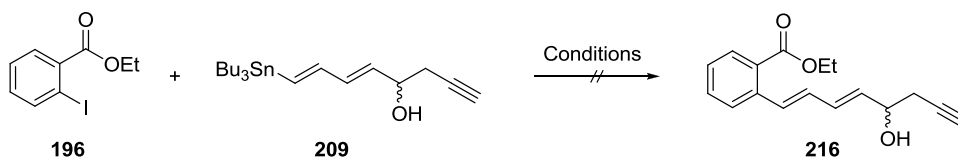
Alternatively, an allenylboronate mediated asymmetric propargylation could be used to prepare the enantiomerically pure (*R*)-alcohol of compound **209**. This reaction was only recently developed for substrates with aldehyde functional groups and was not fully established by the time this work was conducted. Consequently, the number of examples in the literature are limited.²⁵⁴⁻²⁵⁷ Following the procedure by Barnett and Schaus,²⁵⁴ future endeavours to prepare the (*R*)-alcohol of **209** could involve treating the aldehyde **213** with the allenylboronate **215** and BINOL (Scheme 4.14).



Scheme 4.16: Proposed asymmetric propargylation of the aldehyde **213**.

To examine the feasibility of the remaining reactions in the synthesis, *rac*-**209** was used in the subsequent steps. Focusing on the Stille reaction, the iodoester **196** was used as a model compound for the ketoester **197**. Following the conditions by Farina and Roth,²⁵⁸ the iodoester **196** was stirred with compound **209**, Pd(PPh₃)₄ and a catalytic amount of BHT in anhydrous dioxane (Table 4.07, entries 1 and 2).²⁴⁴ BHT was used a radical scavenger to prevent polymerisation of the starting material and the product. Disappointingly, the product was not formed under these conditions. Instead, only starting material was recovered from the reaction. This was also the case when the reaction was repeated in anhydrous dimethylformamide (Table 4.07, entry 3).

Table 4.07: Attempted Stille coupling of the iodoester **196** and compound **209**.



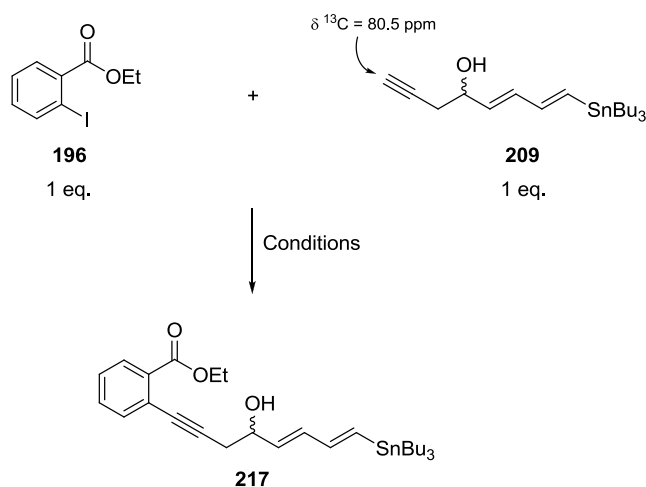
Entry	Conditions	Result
1	Pd(PPh ₃) ₄ (7 mol%), dioxane, BHT (cat.), 25 °C, 12 hrs	no reaction
2	Pd(PPh ₃) ₄ (7 mol%), dioxane, BHT (cat.), 45 °C, 24 hrs	no reaction
3	Pd(PPh ₃) ₄ (7 mol%), DMF, BHT (cat.), 25 °C, 12 hrs	no reaction

4.4 Dual reactivity of compound **209**

In view of these results, an additive to promote the Stille coupling between the iodoester **196** and compound **209** was explored. First reported by Liebekson and Fengel in 1990,²⁵⁹ Cu(I) additives are used to accelerate the Stille coupling of sterically hindered substrates. Studies have shown that Cu(I) has a dual role.²⁶⁰⁻²⁶¹ In ethereal solvents such as tetrahydrofuran and dioxane, Cu(I) acts as a free-ligand scavenger to inhibit autoretardation.²⁵⁹ In solvents such as dimethylformamide and *N*-methyl-2-pyrrolidinone, Cu(I) promotes the formation of an organocuprate species that is more reactive towards transmetallation.²⁵⁸ The addition of a Cu(I) additive could also facilitate the Sonogashira reaction between the terminal alkyne of **209** and the iodoester **196**. Since two competing reactions could occur, a model reaction was investigated to determine the reactivity of the stannane and alkyne functional groups.

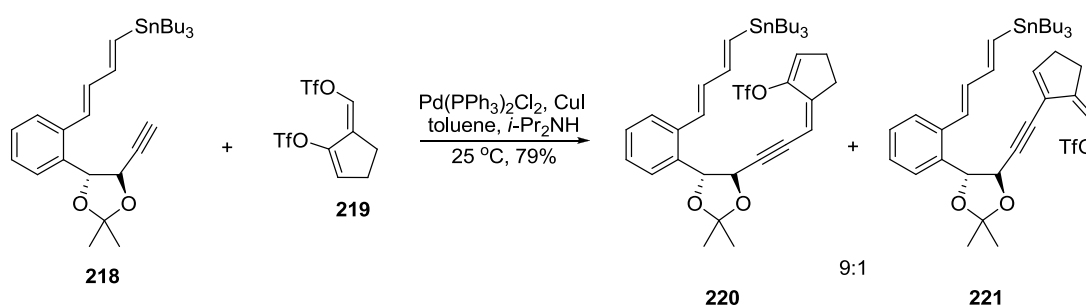
When a mixture of the iodoester **196**, compound **209**, Pd(PPh₃)₄ and BHT in anhydrous dimethylformamide was treated with CuI at 25 °C, a product assigned as the stannane **217** was afforded in 50% yield (Table 4.08, entry 1). The ¹H NMR spectrum of the product showed three signals at 1.47–1.51, 1.26–1.32 and 0.83–0.94 ppm, suggesting the stannane moiety remained intact. The disappearance of the methine signal at 80.5 ppm in the ¹³C NMR spectrum that was ascribed to the terminal acetylenic carbon of compound **209** further supports the synthesis of the Sonogashira product **217**. The high resolution mass spectrum also showed a molecular ion ($m/z = 543.2296$ [M–18 (H₂O)]⁺) that was consistent with the loss of a water molecule for compound **217**. The yield of **217** was improved to 80% by repeating the reaction with piperidine to accelerate the rate of the transmetallation step (Table 4.08, entry 2).²⁶²

Table 4.08: Sonogashira coupling of the iodoester **196** and compound **209**.



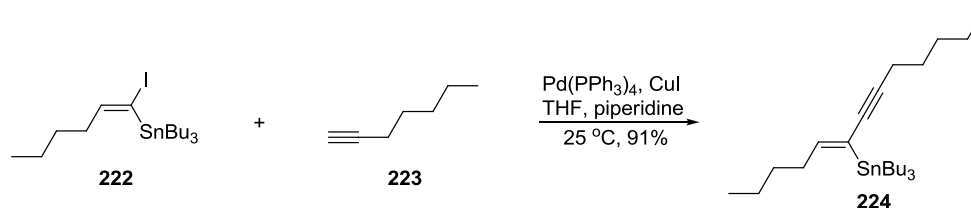
Entry	Conditions	Yield of 217
1	Pd(PPh ₃) ₄ (7 mol%), CuI (10 mol%), DMF, BHT (cat.), 25 °C, 12 hrs	50%
2	Pd(PPh ₃) ₄ (7 mol%), CuI (10 mol%), piperidine (2 eq.), DMF, BHT (cat.), 25 °C, 4 hrs	80%

This is only the third reported coupling reaction that gave the Sonogashira product without forming the Stille product. The first reaction with this unique selectivity was described by Bruckner and co-workers in 2002.²⁶³ Using Pd(PPh₃)₂Cl₂ (4 mol%), CuI (10 mol%) and diisopropylamine, Bruckner afforded the Sonogashira products **220** and **221** as a 9:1 mixture in 79% yield from the alkyne **218** and the triflate **219** (Scheme 4.17).



Scheme 4.17: Bruckner's Sonogashira reaction.²⁶³

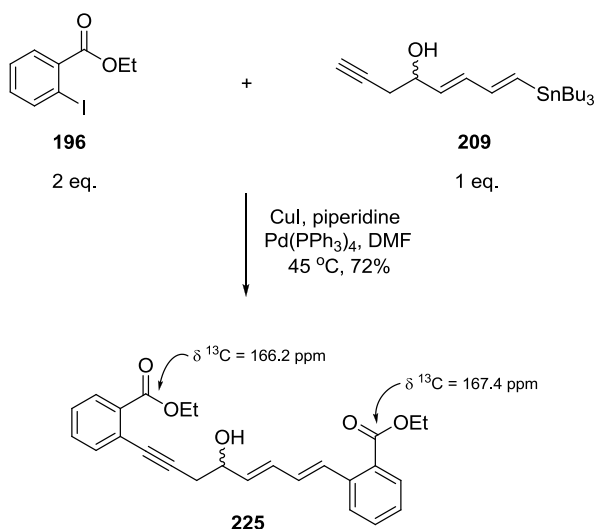
The second reaction was reported by Nazario et al. in 2011.²⁶² Similar to Bruckner's synthesis, the Sonogashira adduct **224** was the only product formed from the reaction between the iodide **222** and 1-heptyne **223** using Pd(PPh₃)₄ (5 mol%), CuI (10 mol%) and piperidine (Scheme 4.18).



Scheme 4.18: Nazario's Sonogashira reaction.²⁶²

One advantage of the reaction described in Table 4.08 was the application of a sterically hindered substrate. Although the iodoester **196** was more hindered than the triflate **219** and the iodide **222**,²⁶²⁻²⁶³ the Sonogashira product **217** was still formed in good yields (80%). This was comparable to the yields of compounds **220**, **221** (79%) and **224** (91%) reported by Bruckner and Nazario.²⁶²⁻²⁶³

Having synthesised compound **217**, the reaction was repeated using two equivalents of the iodoester **196** at 45 °C to probe the reactivity of the stannane functional group (Scheme 4.19). Pleasingly, these changes furnished the Sonogashira-Stille product **225** in 72% yield after 12 hours along with the Sonogashira product **217** in 18% yield. The tandem cross-coupling reaction was supported by the mass spectrum of the product ($m/z = 441.1686$ $[M-18 (H_2O)]^+$) which corresponded with the molecular formula required for the loss of a water molecule of compound **225**. The 1H NMR spectrum of compound **225** showed two signals at 4.41 (4 H) and 1.41 (6 H) ppm, suggesting the presence of two ethyl esters. This was supported by the appearance of two signals at 167.4 and 166.2 ppm in the ^{13}C NMR spectrum that were assigned to the carbonyl carbons of the two esters.

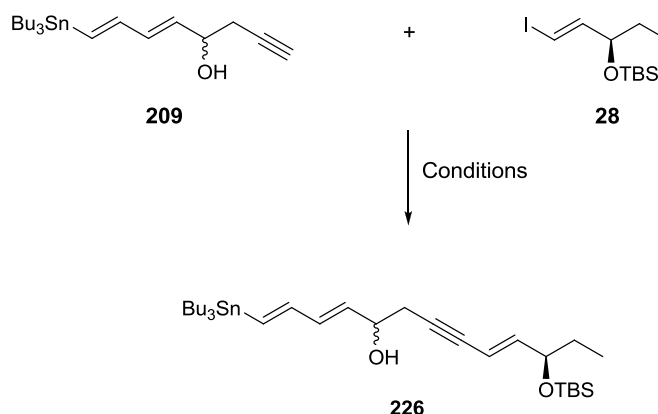


Scheme 4.19: Synthesis of the Sonogashira-Stille product **225**.

4.5 Sonogashira coupling reaction

The application of this result was then applied to the preparation of compound **226**. Following the same conditions outlined in Table 4.08, compound **209** and the iodide **28** were coupled together to afford the Sonogashira product **226** in 51% yield after stirring the reaction mixture at room temperature for 2 hours (Table 4.09, entry 1). Repeating the reaction in anhydrous toluene gave the product in 63% yield (Table 4.09, entry 2). The driving force for the latter reaction was the formation of the piperidine salt that precipitates from toluene. This could account for the increased yield of **226**. Encouragingly, the Stille product was not observed in the ^1H NMR spectrum of the crude reaction mixture when stoichiometric equivalents of compound **209** and the iodide **28** were used.

Table 4.09: Sonogashira reaction with compound **209** and the iodide **28**.



Entry	Conditions	Yield of 226
1	Pd(PPh ₃) ₄ (7 mol%), CuI (10 mol%), piperidine (2 eq.), DMF, BHT (cat.), 25 °C, 2 hrs	51%
2	Pd(PPh ₃) ₄ (7 mol%), CuI (10 mol%), piperidine (2 eq.), toluene, BHT (cat.), 25 °C, 2 hrs	63%

The ¹H NMR spectrum below shows the six vinylic signals of the Sonogashira product **226** (Figure 4.05). These were assigned using coupling constants. The ¹³C NMR spectrum also showed two quaternary signals at 85.7 and 81.7 ppm that were ascribed to the two acetylenic carbons, supporting the synthesis of the internal alkyne.

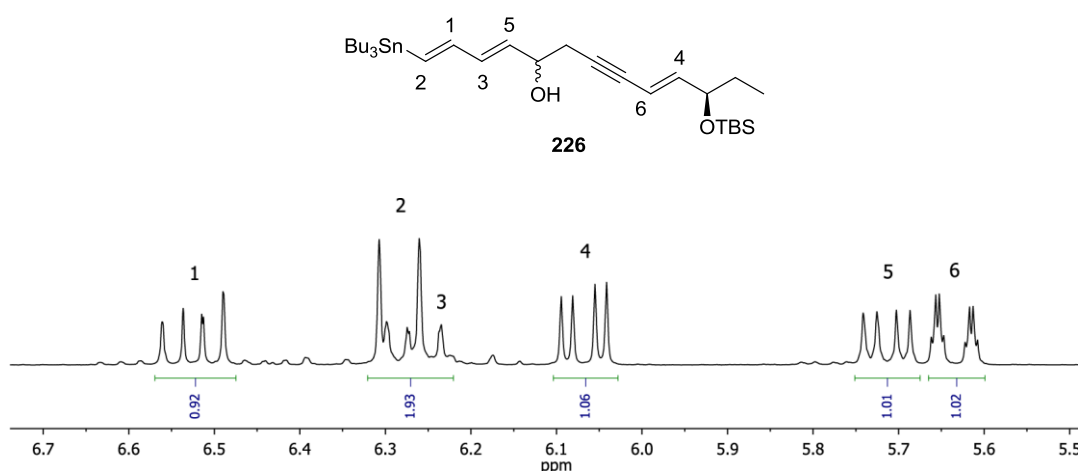
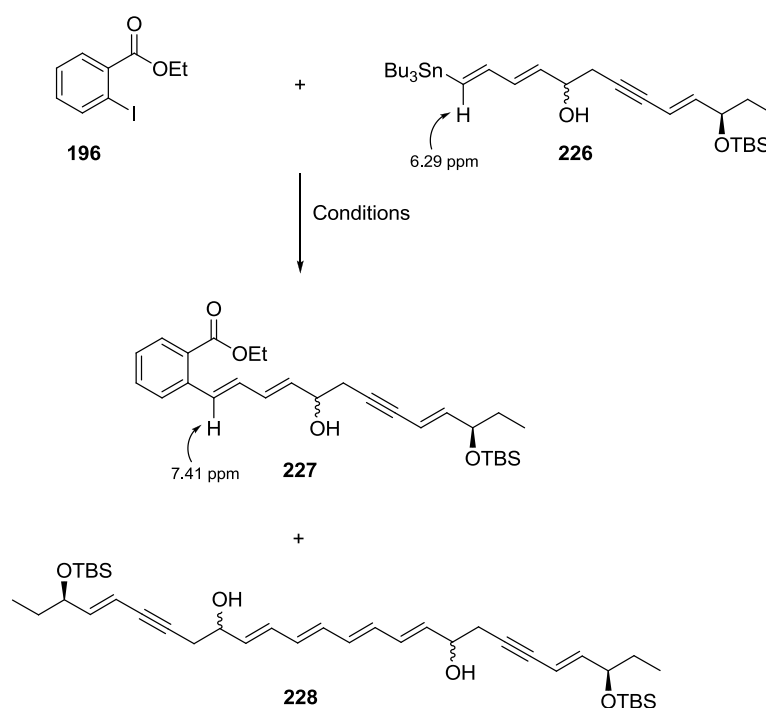


Figure 4.05: ¹H NMR spectrum of compound **226** in CDCl₃ (5.50–6.70 ppm).

To investigate the conditions required to couple the ketoester **197** and compound **226**, the model reaction with compound **196** was revisited. Treatment of the iodoester **196** with compound **226** in anhydrous dimethylformamide at room

temperature gave two new compounds tentatively assigned as **227** and **228** (Table 4.10, entry 1). The first product gave a molecular ion at $m/z = 469.2786$ [M^+] that was consistent with the molecular formula for the Stille adduct **227**. The ^1H NMR spectrum of this compound was missing signals at 0.81–0.97, 1.25–1.36 and 1.48–1.53 ppm, suggesting the loss of the stannane. The vinylic hydrogen of the starting material observed at 6.29 ppm was also replaced with a signal further downfield at 7.41 ppm. This is consistent with the anisotropic effect of the benzene ring.

Table 4.10: Stille reaction with the iodoester **196** and compound **226**.



Entry	Conditions	Result
1	$\text{Pd}(\text{PPh}_3)_4$ (7 mol%), CuI (10 mol%), DMF, BHT (cat.), 25 °C, 12 hrs	227 (20%), 228 (65%)
2	$\text{Pd}(\text{PPh}_3)_4$ (7 mol%), CuI (10 mol%), CH_3CN , BHT (cat.), 25 °C, 12 hrs	227 (48%)
3	$\text{Pd}(\text{PPh}_3)_4$ (2 x 7 mol%), CuI (10 mol%), CH_3CN , BHT (cat.), 25 °C, 72 hrs	227 (51%)

The major product of this reaction was believed to be the dimer **228** based on the ^1H NMR and ^{13}C NMR spectra. The ^1H NMR spectrum of the product showed five vinylic signals between 5.63–6.35 ppm, with a combined integration of twelve hydrogens. Furthermore, seventeen signals were observed in the ^{13}C NMR spectrum, with the six resonances between 108–147 ppm ascribed to the vinylic carbons. Only

six signals were in this region since the dimer **228** is symmetrical. A possible explanation for the formation of **228** was the gradual disproportionation of Cu(I) into Cu(0) and Cu(II). The driving force for this was the formation of a more stable Cu(II)-dimethylformamide complex that facilitates the oxidative coupling of two molecules of stannane **226** to give compound **228**.

To circumvent the dimerisation of the stannane **226**, the reaction was repeated in acetonitrile. Previous studies by Kolthoff and Coetzee have shown that Cu(I) does not disproportionate into Cu(II) and Cu(0) when dissolved in acetonitrile.²⁶⁴ This can be explained with respect to the tetrahedral complex shown in Figure 4.06. By coordinating through the nitrogen donor pairs, acetonitrile forms a Cu[N(CMe)₃]₄I tetrahedral complex. This stabilises the Cu(I) cation so it no longer disproportionates into Cu(II) to mediate the dimerisation of the stannane **226**.

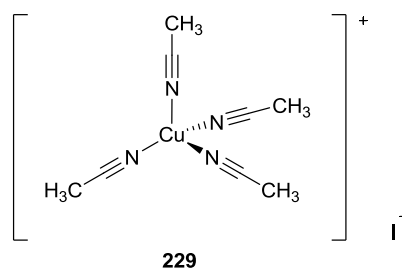
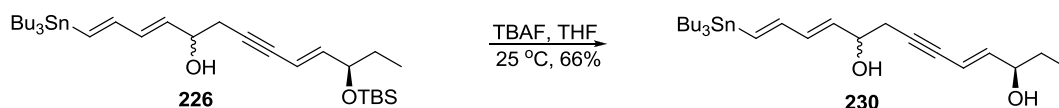


Figure 4.06: Cu(I)-acetonitrile tetrahedral complex **229**.

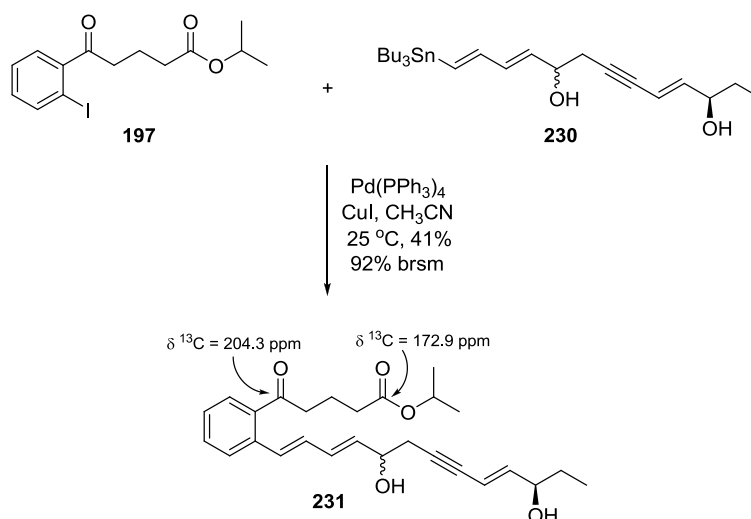
When the reaction was repeated with acetonitrile, the Stille product **227** was furnished in 48% yield and 95% yield based on recovered starting material (Table 4.10, entry 2). Pleasingly, the dimer **228** was not observed in the ¹H NMR spectrum of the crude reaction mixture. Adding another 7 mol% of Pd(PPh₃)₄ after 12 hours and prolonging the reaction time to 72 hours gave compound **227** in 51% yield (Table 4.10, entry 3).

Having optimised the Stille reaction for the model system, attention was focused on the real system. To remove the silyl group, the stannane **226** was treated with TBAF in anhydrous tetrahydrofuran at 25 °C. This afforded compound **230** in 66% yield (Scheme 4.20). The three singlets at 0.90 (9 H), 0.05 (3 H) and 0.03 (3 H) ppm ascribed to the TBS group of the starting material had disappeared. The IR spectrum of the product also showed a broad peak at 3381 cm⁻¹ that was assigned to the two allylic alcohols.



Scheme 4.20: Desilylation of the stannane **226**.

Following the same conditions used in the model reaction, a mixture of the ketoester **197**, compound **230**, $\text{Pd}(\text{PPh}_3)_4$, CuI , BHT and anhydrous acetonitrile was stirred at 25 °C (Scheme 4.21). After one hour, the appearance of a new spot with a lower R_f value than both the starting materials was observed by TLC. The reaction was stirred for a further 11 hours and subjected to column chromatography to give the Stille product **231** as a mixture of C_{12} epimers in 41% yield and 92% yield based on recovered starting material. Similar to compound **227**, both the ^1H NMR and ^{13}C NMR spectra showed no clear distinction between the epimers due to the large distance between the two stereocenters.



Scheme 4.21: Stille reaction between the ketoester **197** and compound **230**.

The ^1H NMR spectrum of the product showed six signals between 5.64–7.01 ppm that were ascribed to the six vinylic hydrogens and three signals between 7.30–7.58 ppm assigned to the four aromatic hydrogens. The resonances at 204.3 and 172.9 ppm observed in the ^{13}C NMR spectrum could be attributed to the ketone and isopropyl ester while the molecular ion at $m/z = 461.2316$ $[\text{M}+23 (\text{Na})]^+$ was consistent with the molecular formula required for $\text{C}_{27}\text{H}_{34}\text{O}_5$.

4.6 Endgame

Having prepared compound **231**, only 3 steps remained in the synthesis of benzo-resolvin E1. These included the reduction of the alkyne and ketone functional groups and hydrolysis of the isopropyl ester (Figure 4.07).

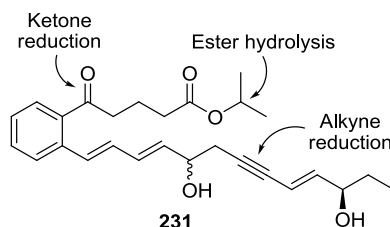
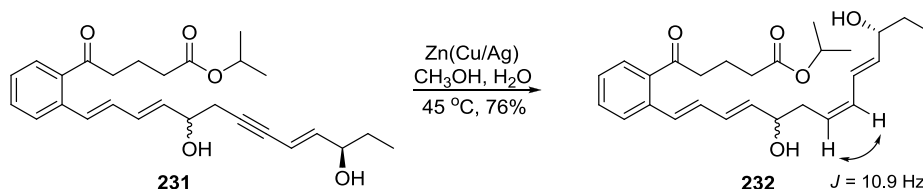


Figure 4.07: Benzo-resolvin E1 endgame.

Following the procedure by Allard (Scheme 1.18),¹⁸² the alkyne of **231** was reduced to a *Z*-alkene using a Zn(Cu/Ag) amalgam.²⁶⁵ This afforded the 14*Z*,16*E*-diene portion of compound **232** (Scheme 4.22). Although the mechanism for the reduction is yet to be established, it is suggested that the reaction proceeds via a radical induced pathway.²⁶⁵



Scheme 4.22: Reduction of the alkyne **231** using a Zn(Cu/Ag) amalgam.

The newly formed alkene was confirmed by the appearance of two vinylic signals at 6.17 and 5.50 ppm in the ¹H NMR spectrum and the disappearance of the two acetylenic carbons at 86.3 and 81.3 ppm in the ¹³C NMR spectrum. The mass spectrum of the product also showed an increase in the *m/z* ratio by two units (*m/z* = 463.2461 [M+23 (Na)]⁺) which was consistent with the molecular formula of compound **232**. The newly formed vinylic hydrogens have a common coupling constant of 10.9 Hz. This is in the range expected for a *Z*-alkene. These hydrogens along with the six other vinylic hydrogens of compound **232** were assigned via a 2D-COSY NMR experiment (Figure 4.08).

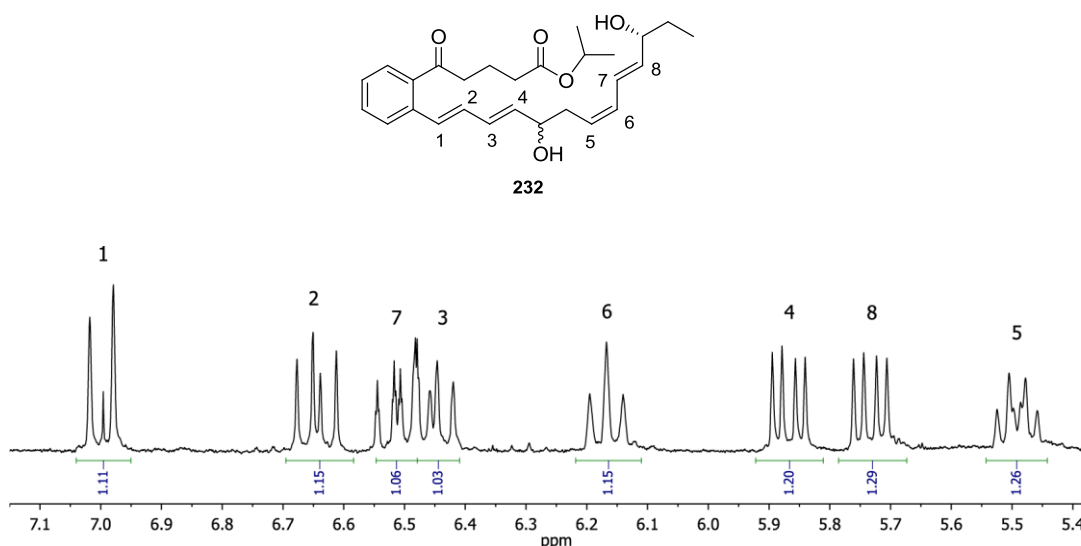
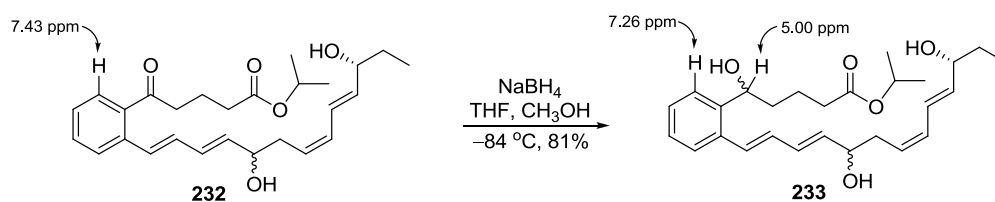


Figure 4.08: ^1H NMR spectrum of compound **232** in CDCl_3 (5.40–7.10 ppm).

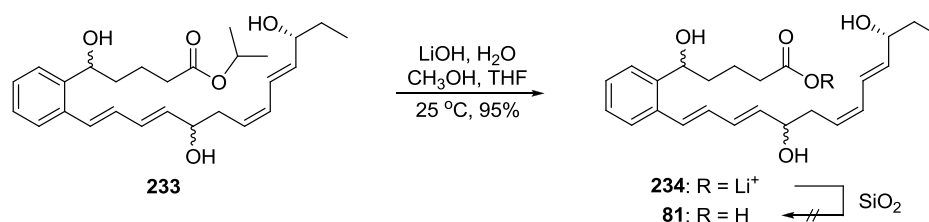
The penultimate step in the synthesis involved the reduction of the ketone. Since the C_5 alcohol readily racemised under normal laboratory conditions (Figure 4.03), the asymmetric reduction of compound **232** was not attempted. Instead, the ketone was reduced with NaBH_4 to give a racemic mixture of the benzyl alcohol (Scheme 4.23). The ^1H NMR spectrum of the product showed the appearance of a resonance at 5.00 ppm ascribed to the benzylic hydrogen while the aromatic resonance at 7.43 ppm was shifted up-field to 7.26 ppm. This change could be attributed to the electron donating effect of the benzyl alcohol.



Scheme 4.23: Reduction of the benzylic ketone using NaBH_4 .

To complete the synthesis of benzo-resolvin E1, the ester was hydrolysed with LiOH (Scheme 4.24). This offered a milder alternative to NaOH , which was used in Allard's synthesis (Scheme 1.18).¹⁸² Gratifyingly, the lithium carboxylate salt of benzo-resolvin E1 was afforded in 95% yield. The synthesis of this compound had the longest linear sequence of 13 steps from 1-pentyn-3-ol **138**, with an overall yield of 2%. The disappearance of the signals at 5.00 and 1.17 ppm in the ^1H NMR spectrum of the product suggests that the isopropyl group was removed. This was

also supported by the molecular ion ($m/z = 407.2422$ [M^+]) observed in the high resolution mass spectrum which was consistent with the molecular formula required for the loss of an isopropyl group. In an attempt to form the free acid of benzoeresolvin E1, compound **234** was passed through silica gel. Surprisingly, an unknown compound was quantitatively recovered, possibly an acid mediated rearranged product. Unfortunately, the structure of this compound could not be determined.



Scheme 4.24: Hydrolysis of compound **233** with LiOH.

The ^1H NMR spectrum of the lithium carboxylate salt of benzoeresolvin E1 showed excellent separation of all the proton resonances (Figure 4.10). These were fully assigned using 2D-NMR techniques. Although the product was formed as a mixture of diastereoisomers, the ^1H NMR and ^{13}C NMR spectra of these compounds were identical. The UV spectrum of the target compound is shown in Figure 4.09. The maximum absorption wavelength was observed at 272 nm. This wavelength is in the region characteristic of a conjugated triene and is consistent with the wavelength maxima ($\lambda_{\text{max}} = 270$ nm) observed for resolvin E1.¹⁷¹

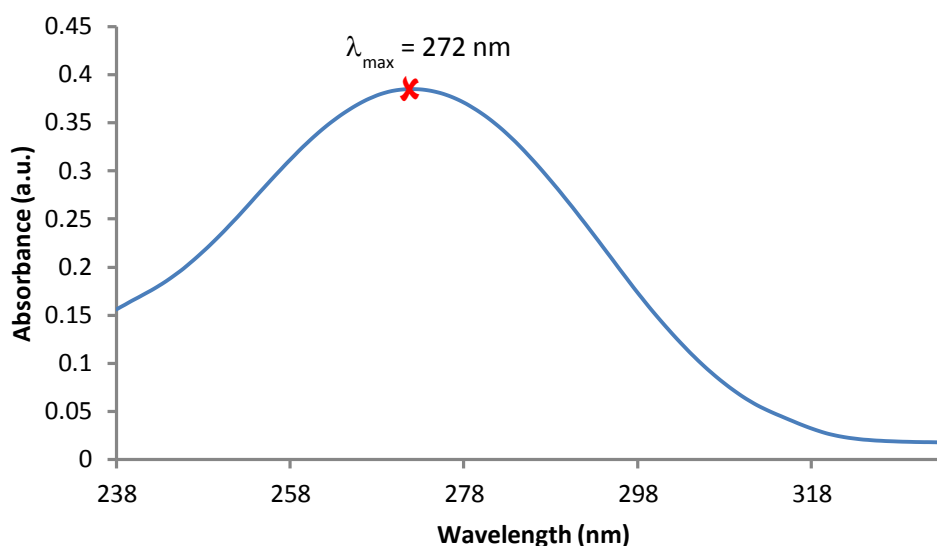


Figure 4.09: UV spectrum of the lithium carboxylate salt of benzoeresolvin E1 in methanol.

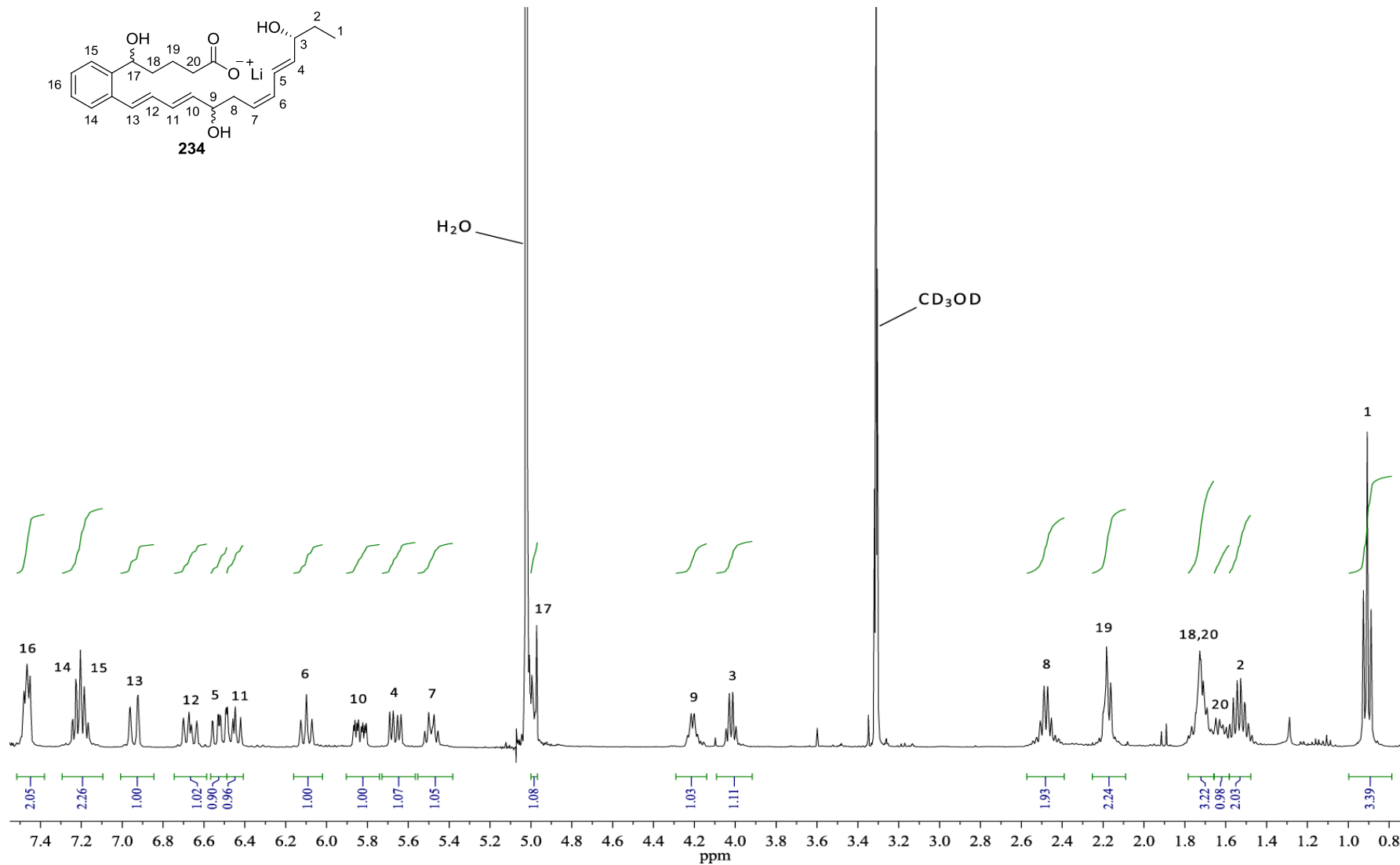


Figure 4.10: ^1H NMR spectrum of the lithium carboxylate salt of benzoeresolvin E1 in CD₃OD.

4.7 Stability study of benzoiresolvin E1

To investigate the stability of the lithium carboxylate salt of benzoiresolvin E1 at 25 °C, a phosphate buffered solution (pH 7.4) of the target compound in D₂O was prepared. The ¹H NMR spectra were obtained over a four day period and the key aromatic and vinylic resonances were compared. The ¹H NMR spectra are shown in Figure 4.12. The signals of interest are at 6.14 and 5.48 ppm. These are ascribed to the vinylic hydrogens of the *Z*-alkene. Pleasingly, these remained unchanged over four days. This suggests that the 14*Z*,16*E*-diene of the terminal chain does not isomerise to the 14*E*,16*E*-diene. No differences were observed for the remaining aromatic and vinylic resonances. Since the diastereoisomers of **234** have the same ¹H NMR spectra, it is unclear if the C₅, C₁₂ or C₁₈ alcohols isomerise under these conditions.

In comparison to the study conducted by Maddapati and Zhou,¹⁹⁵ a solution of resolvin E1 under the same conditions readily led to decomposition. Although the mode of decomposition for resolvin E1 was not reported by Maddapati and Zhou,¹⁹⁵ the ¹H NMR study in Figure 4.12 suggests the chemical stability of this compound could be related to the configuration of the C₆–C₇ alkene. This inference was supported by Kobayashi and Ogawa who claim that the stability of resolvin E1 could be linked to the stability of the 6*Z*-alkene of the triene unit.¹⁸¹ By adding a benzene ring, isomerisation could no longer occur at this position (Figure 4.11). This appears consistent with the ¹H NMR spectra of the target compound in D₂O that remained unchanged over a four day period. Subsequently, the ¹H NMR study suggests that at a physiological pH, the lithium carboxylate salt of benzoiresolvin E1 has a superior chemical stability compared to the parent resolvin E1.

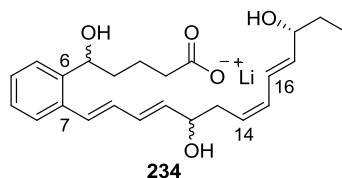


Figure 4.11: Lithium carboxylate salt of benzoiresolvin E1.

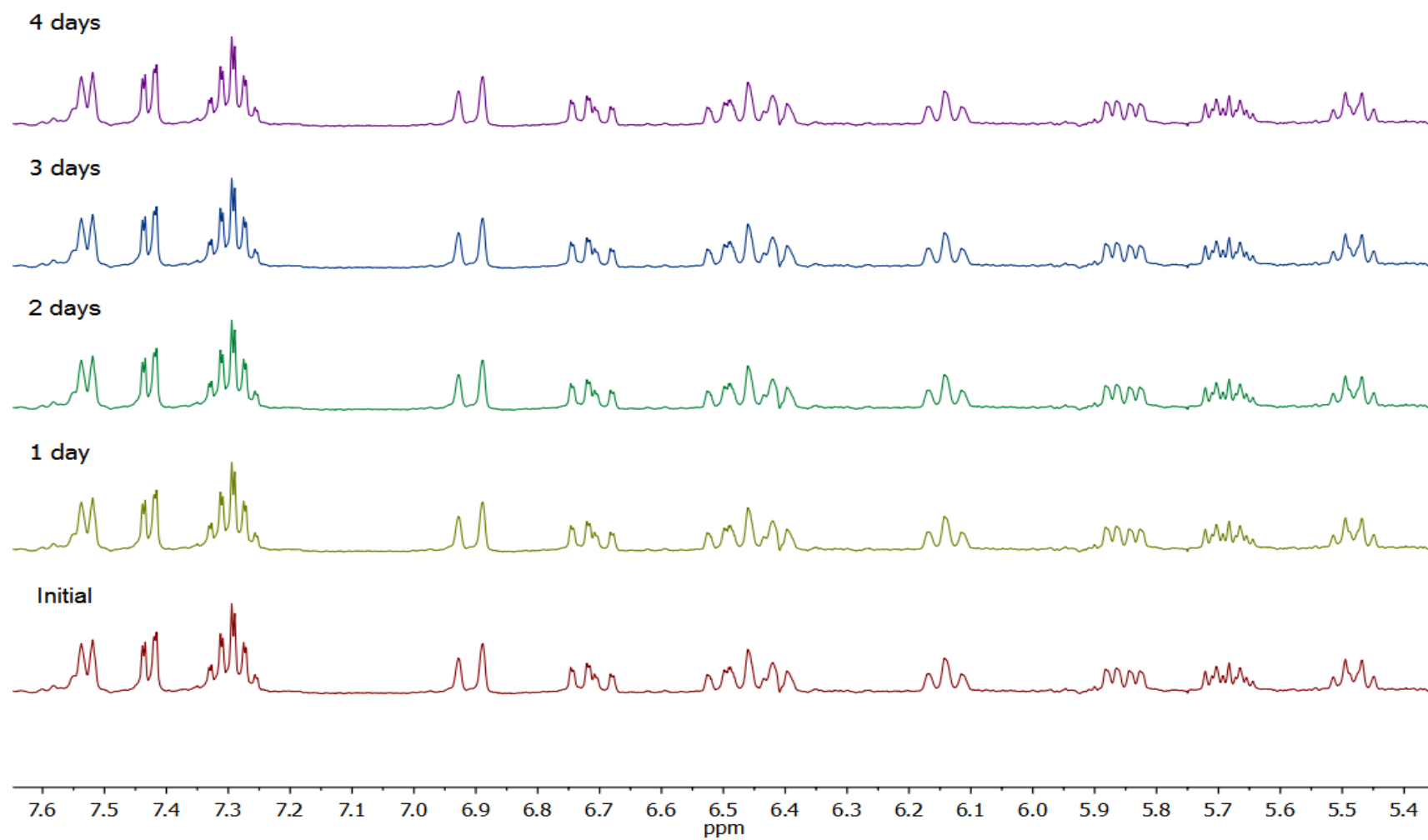


Figure 4.12: ^1H NMR spectra of a phosphate buffered solution of benzo-resolvin E1 in D_2O (5.40–7.60 ppm).

4.8 Inhibition of BLT-1

Using the procedure described by Winkler et al.,²⁶⁶ a radio-ligand binding assay was conducted by Eurofins Panlabs to evaluate the activity of benzoiresolvin E1 towards the BLT-1 receptor. The concentration of benzoiresolvin E1 required to displace 50% of tritium labelled leukotriene B₄ from BLT-1 was 4.14 μ M while the inhibitory constant was 1.05 μ M. These values were compared to other compounds that target the BLT-1 receptor. Compound **235**, also known as SC-41930, is a BLT-1 antagonist that was synthesised in 1989 by Djuric and co-workers (Figure 4.13).²⁶⁷ It has similar anti-inflammatory properties to resolin E1.²⁶⁸⁻²⁶⁹ Studies by Tsai and Penning determined the IC₅₀ and K_i values of **235** to be 4.10 μ M and 1.00 μ M respectively.²⁶⁸⁻²⁶⁹ This is comparable to benzoiresolvin E1, suggesting that both compounds have a similar affinity for the BLT-1 receptor.

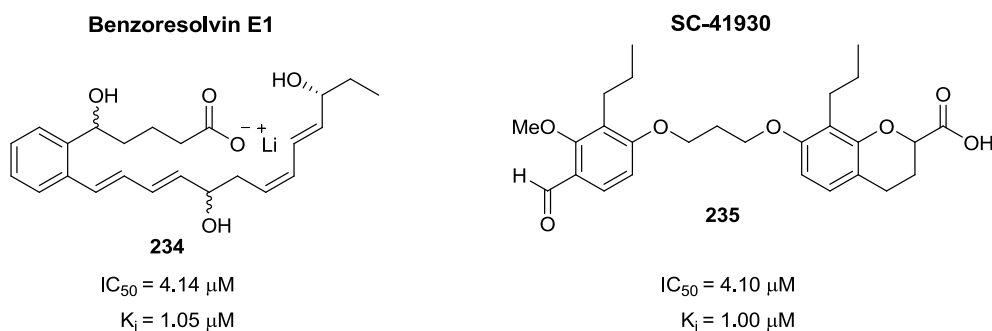


Figure 4.13: A comparison of the IC₅₀ and K_i values for benzoiresolvin E1 and SC-41930.

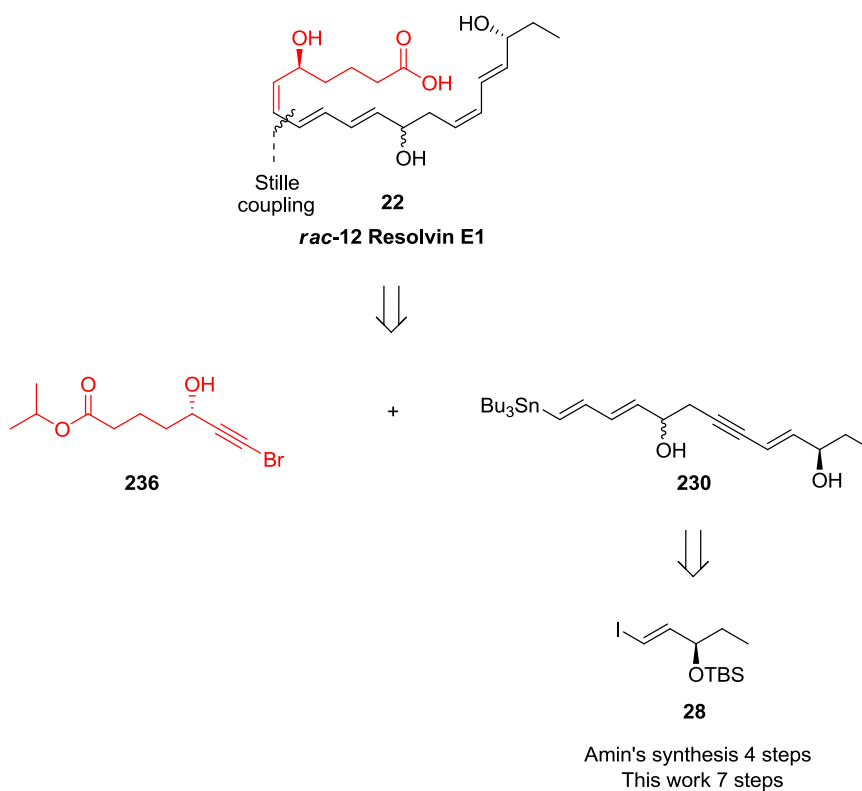
Radio-ligand binding assays carried out by Arita and co-workers showed the enantiomerically pure resolin E1 to have a K_i of 70 nM.¹⁸⁶ This is 15 times lower than the K_i of benzoiresolvin E1, suggesting that resolin E1 has a greater affinity for the BLT-1 receptor. Two reasons could account for this difference. Firstly, this result demonstrates that the fused benzene ring weakens but retains the binding towards the BLT-1 receptor. This could suggest that the hydrophobic pocket at the active site of the receptor may not be large enough to accommodate the benzene ring. Secondly, the target compound is a mixture of the C₅ and C₁₂ diastereoisomers. Assuming one of the diastereoisomers is the active compound and they are all formed in the same amount, it could be speculated that benzoiresolvin E1 has a K_i of 262 nM. Therefore, although purely conjectural, the target compound may only be 4 times less effective at binding to the BLT-1 receptor than resolin E1.

Chapter 5

Formal Total Synthesis of *rac*-12 Resolvin E1

5.1 Retrosynthesis of *rac*-12 resolvin E1

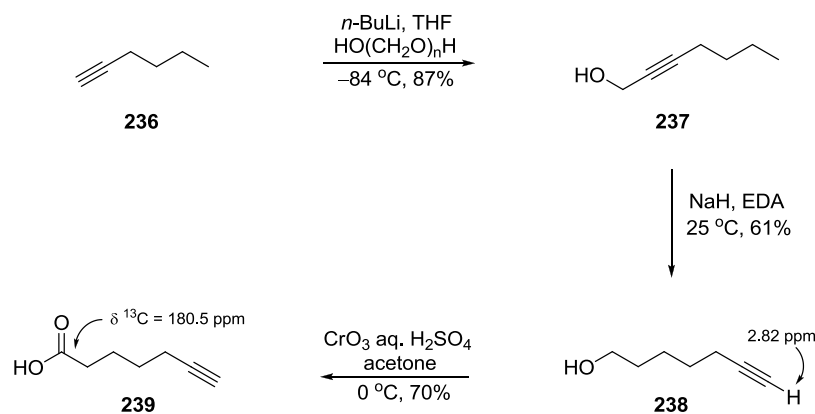
With the synthesis of benzo-resolvin E1 complete, the same cross-coupling strategy was used to prepare *rac*-12 resolvin E1. There are three total syntheses of resolvin E1. These were developed by Petasis, Kobayashi and Allard and are described in Chapter 1.¹⁸⁰⁻¹⁸² For this synthesis, the triene portion of the target compound could be formed by a Stille reaction between the bromo-acetylide **236** and the stannane **230** (Scheme 5.01). Unlike the other procedures, an advantage of this synthesis is the limited use of protecting groups. If Amin's procedure was used to prepare fragment **28**,¹⁸⁵ the planned route would also be the shortest linear synthesis of resolvin E1 to date. Having prepared compound **230**, attention was focused on the synthesis of the bromo-acetylide **236**.



Scheme 5.01: Retrosynthesis of *rac*-12 resolvin E1.

5.2 Preparation of the bromo-acetylide **236**

The starting material for the synthesis of the bromo-acetylide **236** was 1-heptyne **236** (Scheme 5.02). Deprotonation of the acetylenic hydrogen with *n*-BuLi followed by the addition of paraformaldehyde afforded compound **237** in 87% yield.²⁷⁰ Isomerisation of the internal alkyne **237** to the terminal alkyne **238** was performed using a Zipper reaction. Treatment of **237** with NaH in 1,2-ethylenediamine gave **238** in 61% yield (Scheme 5.02). The driving force for this reaction is the formation of the acetylide anion which remained localised at the terminal position. The ¹H NMR spectrum of the product matched the spectrum reported by Matovic,²⁷¹ with the diagnostic signal at 2.82 ppm ascribed to the newly formed acetylenic hydrogen. Oxidation of the primary alcohol was achieved using Jones reagent at 0 °C, giving the carboxylic acid **239** in 70% yield (Scheme 5.02).

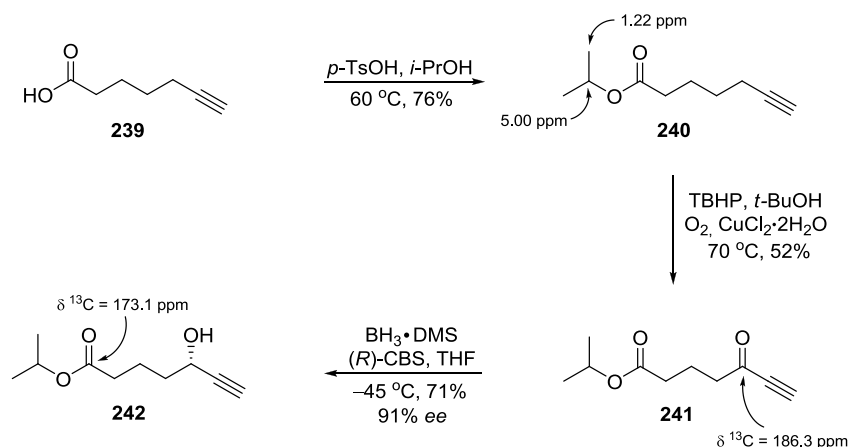


Scheme 5.02: Preparation of compound **239**.

The carboxylic acid of **239** was esterified with isopropyl alcohol and catalytic amounts of *p*-toluenesulfonic acid to afford the ester **240** in 76% yield (Scheme 5.03). The ¹H NMR spectrum of the product showed the appearance of two resonances at 5.00 and 1.22 ppm that were ascribed to the newly formed isopropyl ester. Oxidation of the propargylic position was then achieved using the copper(II) catalysed method described by Li and co-workers.²⁷² This radical initiated process involved the treatment of compound **240** with *t*-butyl hydroperoxide, CuCl₂•2 H₂O and O₂. The reaction was stopped after 24 hours to afford compound **241** in 52% yield and starting material in 44% yield (Scheme 5.03). Stirring the reaction mixture for an additional 24 hours did not increase the yield of compound **241**. The

appearance of a new resonance at 186.3 ppm in the ^{13}C NMR spectrum of the product was consistent with the newly formed ketone.

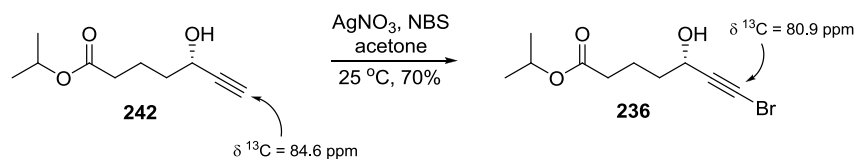
Using the same conditions as described in Table 4.02, the ketoester **241** was treated with borane dimethyl sulfide and (*R*)-CBS catalyst to give the (*S*)-alcohol **242** in 71% yield (Scheme 5.03). The reaction was chemoselective, with the isopropyl ester not reduced under these conditions. This was supported by the ^{13}C NMR spectrum of the product which showed the loss of the ketone resonance at 186.3 ppm. The key signal at 173.1 ppm that was assigned to the carbonyl of the ester was still present. To determine the absolute configuration of the product, the specific rotation was compared to a literature value.²⁷³ The specific rotation of the product was -9.40 ($c = 1.00$, CHCl_3). At the same temperature, Heiss and co-workers reported the (*R*)-enantiomer of alcohol **242** to have a specific rotation of $+10.30^\circ$ ($c = 2.60$, CHCl_3). A comparison of these values indicates that the product was the desired (*S*)-enantiomer and was afforded in 91% *ee*.



Scheme 5.03: Preparation of the (*S*)-alcohol **242**.

The final step in the synthesis of the bromo-acetylide **236** was an acetylenic bromination reaction. Treatment of compound **242** with *N*-bromosuccinimide and silver nitrate in acetone afforded **236** in 70% yield (Scheme 5.04). The diagnostic signal in the ^{13}C NMR spectrum of the product is at 80.9 ppm. This is a quarternary carbon and was ascribed to the acetylenic carbon bearing the bromide. In comparison, only a methine signal at 84.6 ppm was observed in the ^{13}C NMR spectrum of the starting material. The molecular ion at $m/z = 285.0108$ $[\text{M}+23 (\text{Na})]^+$

shown in the high resolution mass spectrum was also consistent with the molecular formula required for $C_{10}H_{15}BrO_3$.

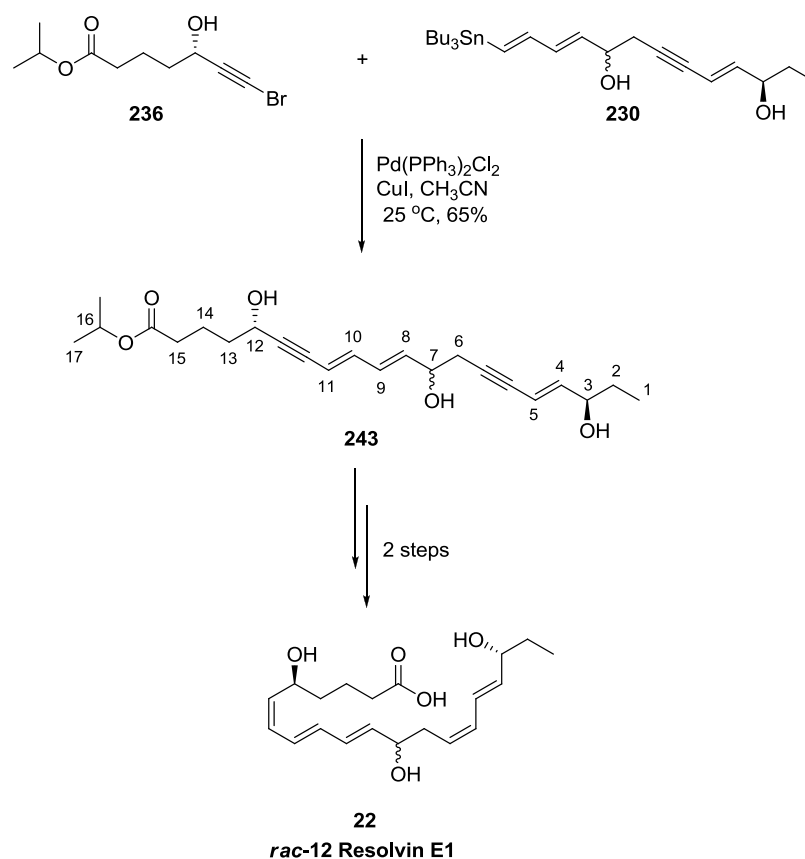


Scheme 5.04: Synthesis of the bromo-acetylide **236**.

5.3 Synthesis of the key intermediate **243**

To prepare the triene portion of *rac*-12 resolvins E1, compound **236** was subjected to a Stille reaction with the stannane **230**. Treatment of these compounds with $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ and CuI in anhydrous acetonitrile afforded the Stille product **243** in 65% yield as a mixture of C_{12} epimers (Table 5.01). Although the product was a mixture of epimers, the ^1H NMR and ^{13}C NMR spectra of these compounds were identical and showed no splitting of the signals. The ^1H NMR spectrum of the product matched the spectroscopic data reported in the literature (Table 5.01).¹⁸² The spectrum showed three resonances at 4.45, 4.26 and 3.97 ppm that were ascribed to the three hydroxyl bearing methine hydrogens and five signals between 5.67–6.58 ppm with an integration of six hydrogens. These were assigned to the six vinylic hydrogens. The ^{13}C NMR spectrum of the product was also consistent with the structure of **243**, with a signal at 174.8 ppm attributed to the carbonyl of the ester while the six signals in the range of 110–146 ppm were assigned to the six vinylic carbons. The product intersects the total synthesis of resolvins E1 developed by Allard and was only 2 steps from the target compound.¹⁸² These steps involved the reduction of the two alkynes to the *Z*-alkenes and hydrolysis of the isopropyl ester. Thus using a Stille coupling approach, the formal total synthesis of *rac*-12 resolvins E1 was completed.

Table 5.01: ^1H NMR signals for *rac*-12 **243** in CD_3OD compared to the literature.¹⁸²



Signal	Stille product*		Literature product*	
	Chemical Shift (ppm)	Multiplicity	Chemical Shift (ppm)	Multiplicity
1	0.91	t	0.91	t
2	1.51	m	1.54	m
3	3.97	q	3.97	q
4	6.00	dd	6.01	dd
5	5.67	m	5.67	m
6	2.52	ddd	2.51	ddd
7	4.26	q	4.25	q
8	5.89	dd	5.88	dd
9	6.35	dd	6.35	dd
10	6.58	dd	6.57	dd
11	5.67	m	5.67	m
12	4.45	t	4.45	t
13	1.65	m	1.64	m
14	2.33	t	2.33	t
15	1.75	m	1.79	m
16	5.00	sp	4.97	sp
17	1.23	d	1.23	d

* The ^1H NMR spectra were recorded at 400 MHz for **243** and 500 MHz for the literature compound.

Chapter 6

Synthesis of a C₁₈-Phenyl Analogue of Benzoeresolvin E1

6.1 C₁₈-Phenyl analogue 244

As benzoeresolvin E1 was shown to bind to the BLT-1 receptor, analogues of this compound were targeted. The C₁₈–C₂₀ terminal portion of benzoeresolvin E1 **234** could be substituted with a phenyl ring to give compound **244** (Figure 6.01). The phenyl ring would remove the alcohol at the C₁₈ position, thus simplifying the synthesis of the target compound. It is yet to be determined if this alcohol plays a role in activating the BLT-1 and ChemR23 receptors. Molecular modelling studies suggest the alcohol could partake in hydrogen bonding with the surrounding amino acid residues at the receptor site (Figure 1.15). Substituting the alcohol with a phenyl ring would sever these interactions. It would also improve the hydrophobic interactions, such as π - π stacking, with the surrounding residues. These interactions may be more effective than the hydrogen bonding, thus improving the binding affinity of the molecule. Subsequently, the inclusion of a phenyl ring at the terminal chain may prolong the anti-inflammatory action of the molecule.

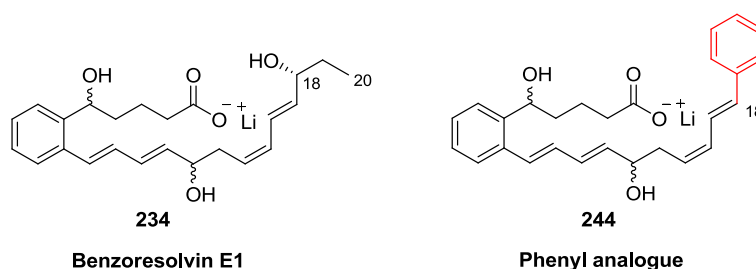


Figure 6.01: Benzoeresolvin E1 **234** and the C₁₈-phenyl analogue **244**.

An example of a phenyl substituted anti-inflammatory was illustrated by Gjørstrup.²⁷⁴ Through structure-activity relationship studies, Gjørstrup showed compound **246** to be a superior agonist compared to the precursor **245** (Figure 6.02).²⁷⁴ These compounds target the liver X receptor (LXR) and retinoic acid receptor (RAR), both of which are responsible for cholesterol and fatty acid metabolism.²⁷⁴ The addition of the phenyl ring increased the lipophilicity of

compound **246**. This improved the hydrophobic interactions at the receptor site, thus increasing the efficacy of the agonist. A similar finding could be observed for the target compound **244**.

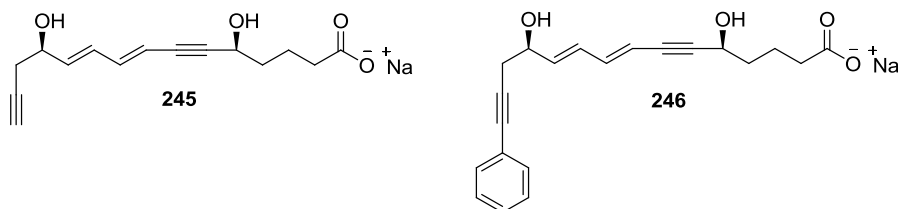
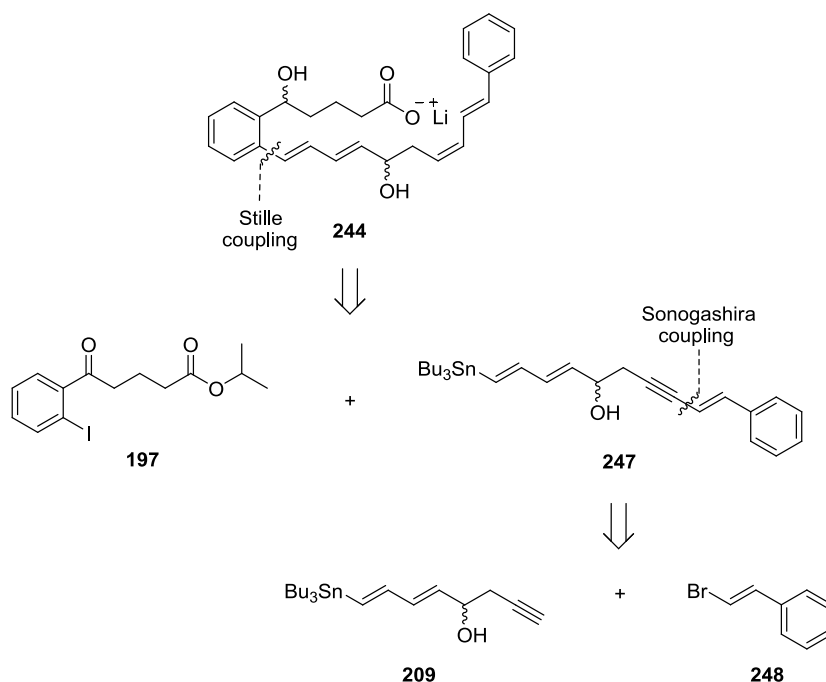


Figure 6.02: LXR and RAR agonists synthesised by Gjorstrup.²⁷⁴

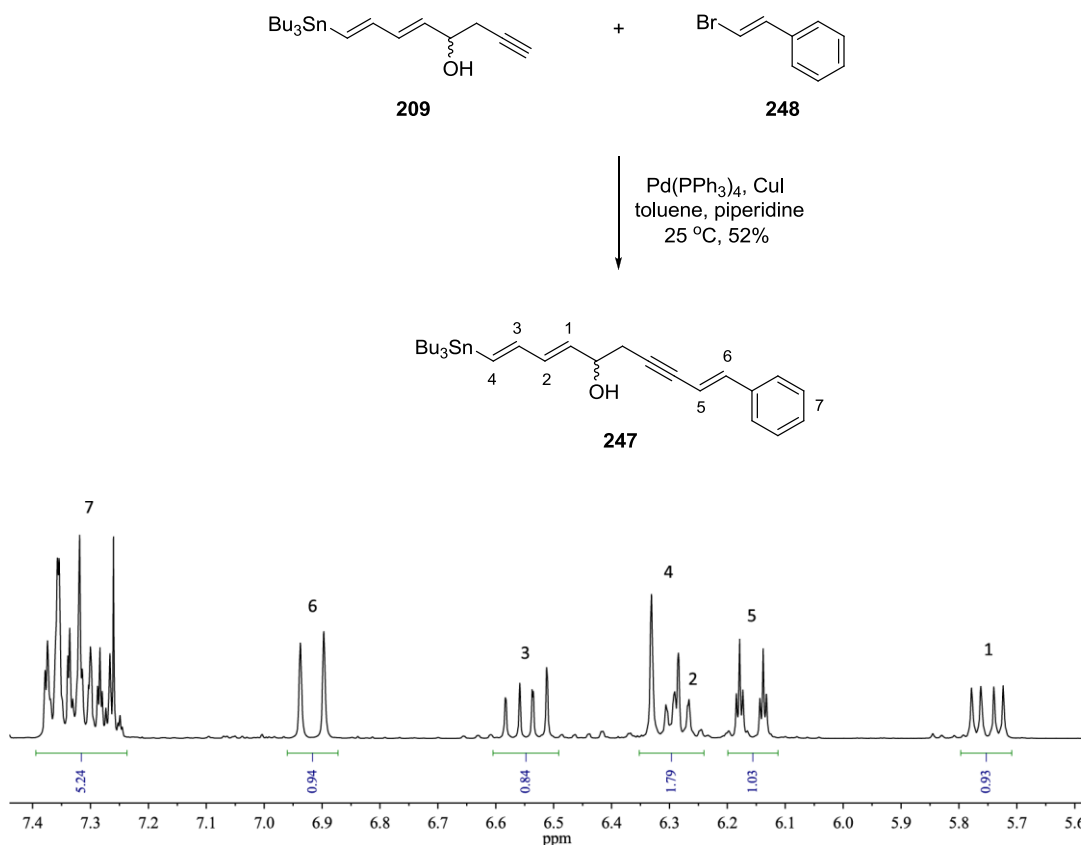
6.2 Retrosynthesis of compound **244**

The target compound **244** could be prepared using the same cross-coupling strategy for benzoiresolvin E1 (Scheme 6.01). A Sonogashira reaction between *rac*-**209** and the bromide **248** could afford the key intermediate **247**. This compound could be coupled with the iodide **197** to give the benzodiene portion of the target compound. Following the same approach as Allard for the synthesis of resolvin E1,¹⁸² the alkyne and the ketone could be reduced and the isopropyl ester hydrolysed to furnish the C₁₈-phenyl analogue of benzoiresolvin E1.



Scheme 6.01: Retrosynthesis of the C₁₈-phenyl analogue **244**.

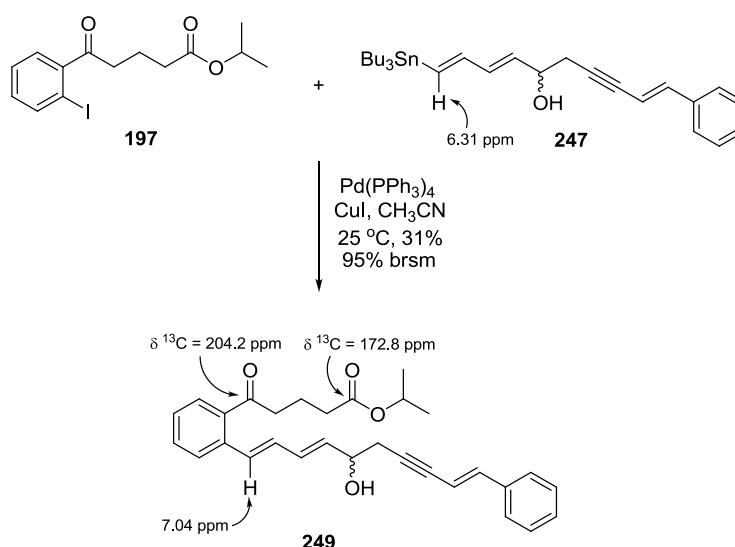
Starting from *trans*-cinnamic acid, the bromide **248** was synthesised in 82% yield via a vinylogous Hunsdiecker reaction.²⁷⁵ The ¹H NMR spectrum of the product showed two new doublets at 7.22 and 6.86 pm with a coupling constant of 14.0 Hz. These are consistent with the vinylic signals of **248** reported by Kuang.²⁷⁵ Following the conditions given in Table 4.08, the alkyne **209** was coupled with compound **248**. This gave the Sonogashira product **247** in 52% yield after stirring the reaction mixture for 7 hours at room temperature (Scheme 6.02). Six new resonances between 5.74–6.91 ppm were observed in the ¹H NMR spectrum of the product. These had coupling constants within the range of 15.5–18.6 Hz, supporting the three *E*-alkenes of **247** (Scheme 6.02). A cluster of signals with an integration of five hydrogens was also observed between 7.27–7.38 ppm. These were attributed to the aromatic hydrogens.



Scheme 6.02: Synthesis of compound **247**.

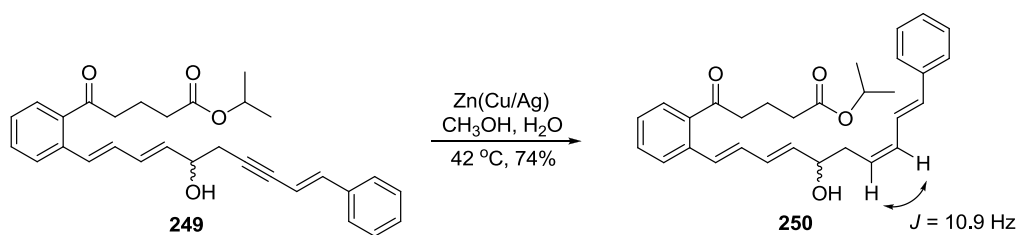
The stannane **247** was then treated with the iodide **197**, Pd(PPh₃)₄, CuI and BHT in anhydrous acetonitrile (Scheme 6.03). After stirring the reaction mixture for 12 hours at room temperature, the Stille product **249** was formed in 27% yield and 95% yield based on recovered starting material. A longer reaction time of 3 days

afforded the product in 31% yield. The low yields could be attributed to the poor solubility of the stannane **249** in acetonitrile. Despite this result, a change in the solvent was not necessary since the unreacted starting material was recovered in near quantitative yields. The diagnostic signal in the ^1H NMR spectrum of the product was at 7.04 ppm. This was ascribed to the vinylic hydrogen adjacent to the benzene ring and was downfield to the vinylic hydrogen of compound **247** shown at 6.31 ppm. This is consistent with the anisotropic effect of the benzene ring. The ^{13}C NMR spectrum also showed two signals at 204.2 and 172.8 ppm that could be assigned to the ketone and ester functional groups.



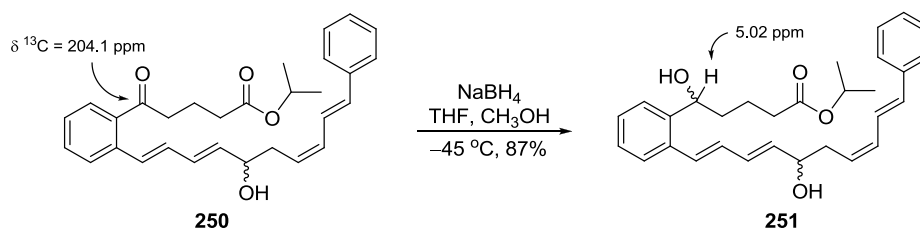
Scheme 6.03: Stille coupling between the iodide **197** and compound **247**.

The next step in the synthesis involved the reduction of the alkyne to give the 14*Z*,16*E*-benzodiene terminal chain. Treatment of compound **249** with a freshly prepared Zn(Cu/Ag) amalgam²⁶⁵ gave the isometrically pure *Z*-alkene **250** in 74% yield (Scheme 6.04). The reduction of the alkyne was confirmed by the mass spectrum ($m/z = 481.2372$ $[\text{M}+23(\text{Na})]^+$) which was two m/z units higher than the starting material. The ^1H NMR spectrum showed two resonances at 5.57 and 6.34 ppm that were ascribed to the newly formed vinylic hydrogens (Scheme 6.04). These hydrogens have a common coupling constant of 10.9 Hz and are indicative of a *Z*-alkene.



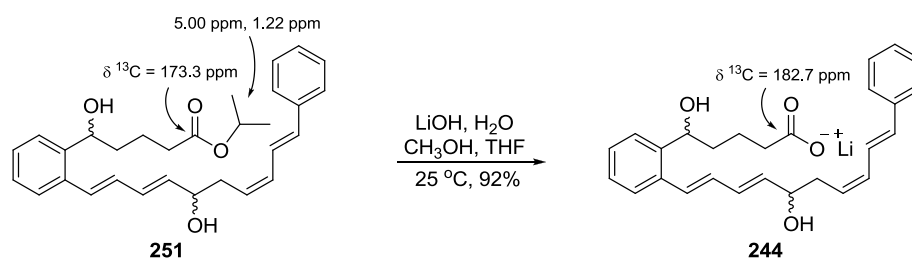
Scheme 6.04: Reduction of the alkyne **249** using a Zn(Cu/Ag) amalgam.

Having selectively reduced the alkyne, attention was focused on the reduction of the ketone. Treatment of compound **250** with 2.5 equivalents of NaBH₄ at $-45\text{ }^{\circ}\text{C}$ afforded the diol **251** in 87% yield (Scheme 6.05). Compound **251** was isolated as a mixture of diastereoisomers that could not be separated by column chromatography. The product obtained from the reaction did not have a ketone. This was validated by the disappearance of the carbonyl signal at 204.1 ppm in the ^{13}C NMR spectrum. The ^1H NMR spectrum also showed a new resonance at 5.02 ppm that was ascribed to the newly formed benzylic hydrogen (Scheme 6.05).



Scheme 6.05: Reduction of the ketone **250**.

To complete the synthesis of the target compound, the isopropyl ester was hydrolysed with LiOH (Scheme 6.06). This gave the product **244** in 92% yield. The synthesis of this compound had the longest linear sequence of 11 steps from *o*-iodobenzoic acid, with an overall yield of 5%. The disappearance of the signals at 5.00 and 1.22 ppm in the ^1H NMR spectrum and the resonance at 173.3 ppm in the ^{13}C NMR spectrum suggest the isopropyl group had been removed. A molecular ion was also observed at $m/z = 425.2324$ $[\text{M}+23(\text{Na})]^+$ in the high resolution mass spectrum which was consistent with the molecular formula required for the loss of an isopropyl group.



Scheme 6.06: Hydrolysis of the isopropyl ester **251**.

Similar to benzoeresolvin E1, the ^1H NMR spectrum of the C_{18} -phenyl analogue **244** showed excellent separation of all the proton resonances (Figure 6.04). These were fully assigned using 2D-NMR techniques. Although the product was formed as a mixture of diastereoisomers, the ^1H NMR and ^{13}C NMR spectra of these compounds were identical. The UV spectrum of the product is shown in Figure 6.03. The maximum absorption wavelength was observed at 281 nm. This wavelength is in the region characteristic of a benzodiene and is similar to the wavelength maxima observed for benzoeresolvin E1.

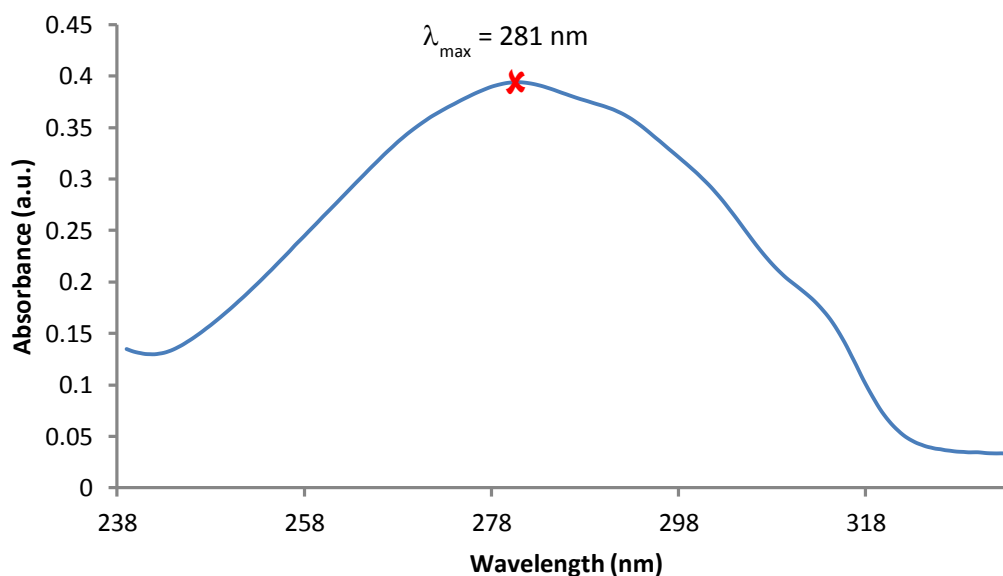


Figure 6.03: UV spectrum of the C_{18} -phenyl analogue **244** in methanol.

6.3 Inhibition of BLT-1

To evaluate the activity of the C₁₈-phenyl analogue **244** towards the BLT-1 receptor, a radio-ligand binding assay was conducted by Eurofins Panlabs using the procedure described by Winkler et al.²⁶⁶ The assay showed **244** binds to the receptor with 68% activity at a concentration of 10 μ M. This is lower than benzoiresolvin E1 which has an activity of 76% at the same concentration.²⁶⁶ This result demonstrates that the C₁₈-phenyl substituent does not significantly reduce the binding affinity of the molecule compared to the C₁₈-alcohol of benzoiresolvin E1. Consequently, a hydrogen donor group at this position is important but not essential for enhancing the binding affinity of the molecule.

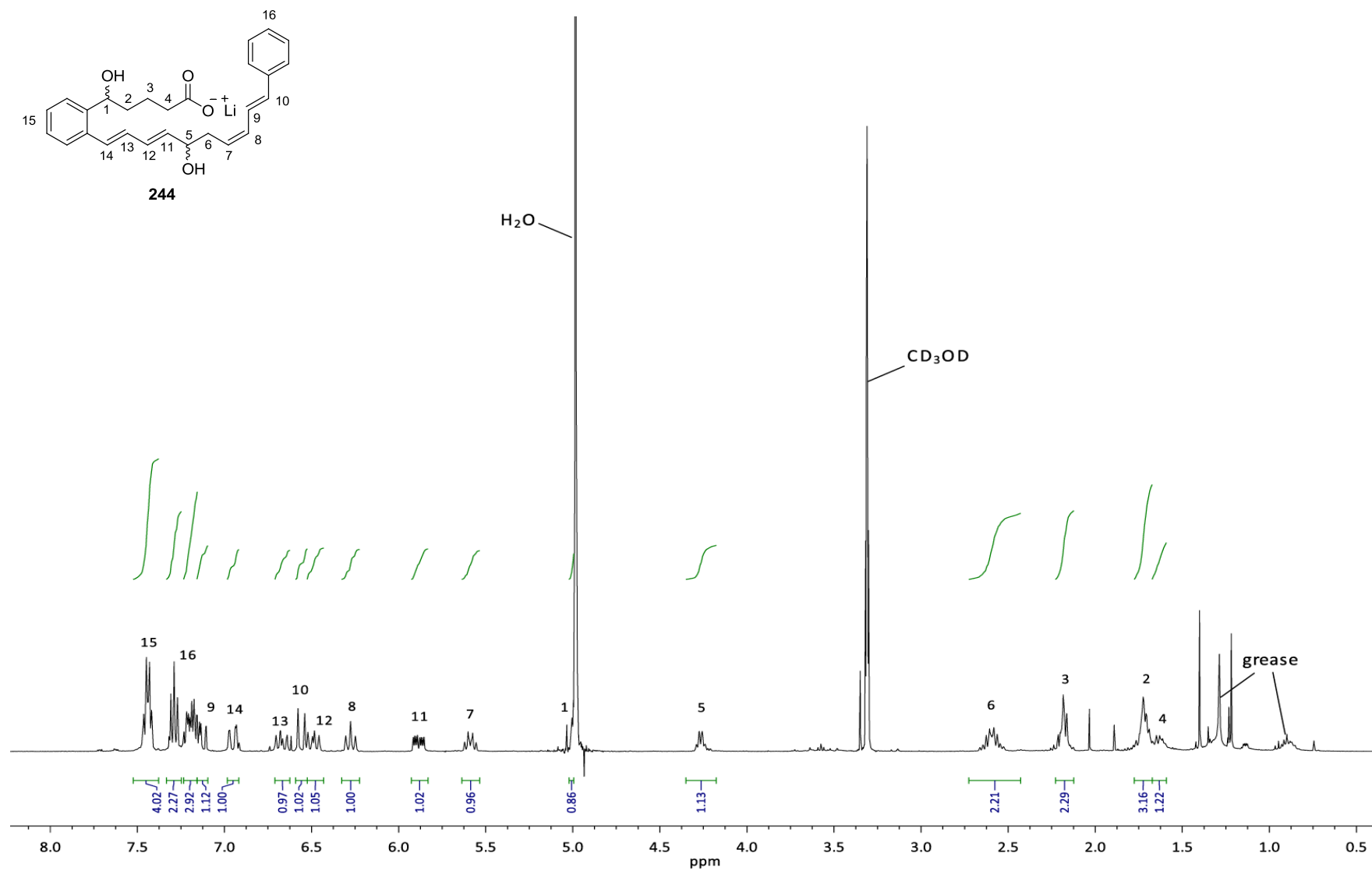


Figure 6.04: ¹H NMR spectrum of the C₁₈-phenyl analogue **244** in CD₃OD.

Chapter 7

Synthesis of Benzoleukotriene B₄

7.1 Leukotriene B₄ and benzoleukotriene B₄

In Chapter 4, a radio-ligand binding assay was undertaken to investigate the activity of benzoiresolvin E1. The results showed that benzoiresolvin E1 competed with tritium labelled leukotriene B₄ to bind to the BLT-1 receptor. Leukotriene B₄ is a pro-inflammatory lipid mediator and is an agonist of this receptor.¹⁸⁷ Unlike resolvin E1, leukotriene B₄ facilitates the recruitment of neutrophils, monocytes and eosinophils.¹⁸⁷ It also stimulates the production of pro-inflammatory cytokines such as IL-4, IL-5, IL-6, IL-8 and IL-10.^{18,269-270} It was envisaged that a benzene annulated analogue of leukotriene B₄, herein named benzoleukotriene B₄, would also bind to the BLT-1 receptor. In view of this, the following chapter details investigations towards this compound.

There are two key differences between benzoiresolvin E1 and leukotriene B₄. The first difference is the C₁₆–C₂₀ terminal chain (Figure 7.01, blue). Unlike benzoiresolvin E1 which has an allylic alcohol at the C₁₈ position, leukotriene B₄ has a pentyl chain. This portion of the molecule is thought to fit in a long pocket at the active site of the BLT-1 receptor, thus improving the binding affinity of the molecule through hydrophobic interactions.¹⁸⁷ Secondly, benzoiresolvin E1 has a benzene-annulated ring at the C₆–C₇ position (red). This was shown to improve the stability of resolvin E1 by blocking the isomerisation pathway (Figure 4.11). A benzene ring fused at the same position on leukotriene B₄ could also have the same effect.

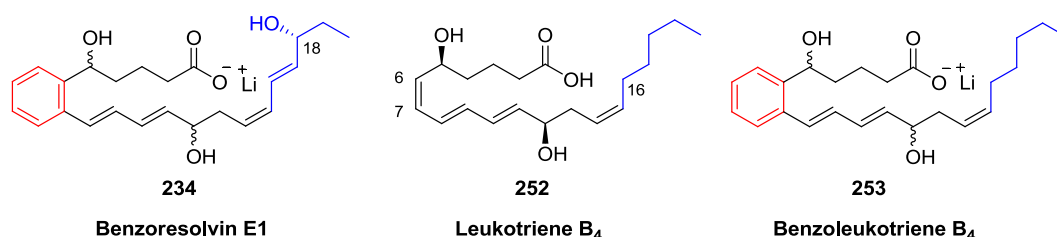
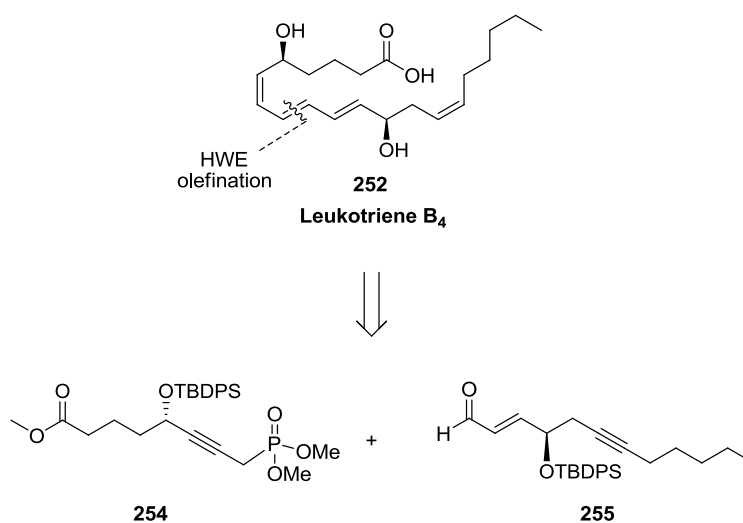


Figure 7.01: Benzoiresolvin E1, leukotriene B₄ and benzoleukotriene B₄.

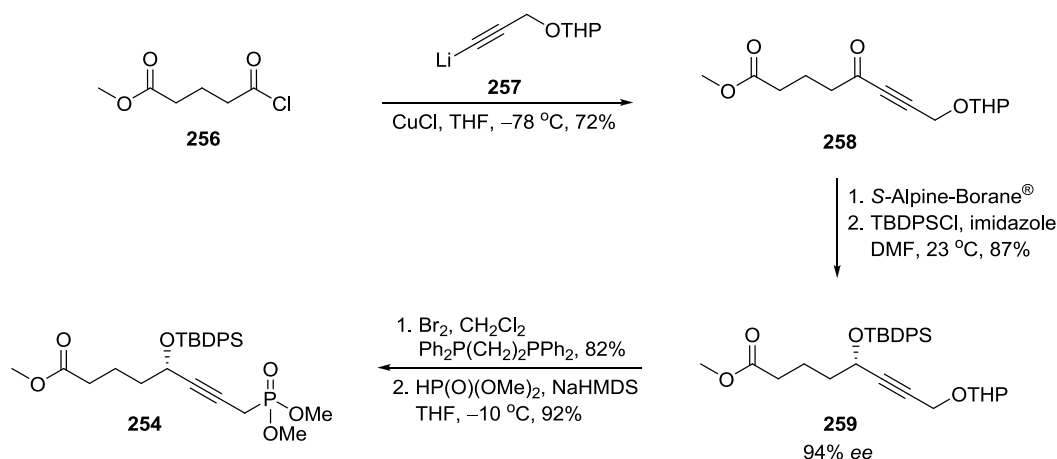
7.2 Total synthesis of leukotriene B₄

There are 11 total syntheses of leukotriene B₄, two of which are selected for review.²⁷⁶⁻²⁸⁶ A common approach to prepare the triene unit of leukotriene B₄ was a Horner-Wadsworth-Emmons olefination. This strategy was used in five of the reported total syntheses.²⁷⁶⁻²⁸⁰ One example is shown in the retrosynthesis developed by Kerdesky and co-workers in 1993.²⁷⁶ The key intermediates in this synthesis are compounds **254** and **255**. These were coupled together to give the 8*E*-alkene of the target compound (Scheme 7.01).



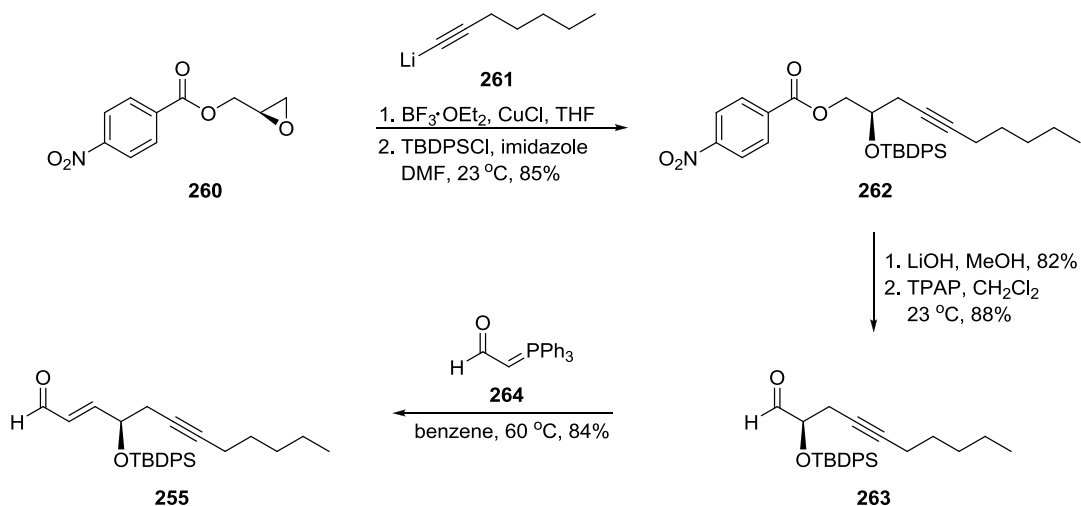
Scheme 7.01: Retrosynthesis of leukotriene B₄ developed by Kerdesky.²⁷⁶

The starting point for the synthesis of compound **254** was 4-chloroformylbutanoate **256** (Scheme 7.02). Addition of the organolithium reagent **257** to this compound gave the alkylated product **258** in 72% yield. The ketone **258** was reduced to the (*S*)-alcohol in 94% *ee* using *S*-Alpine-Borane[®] and the secondary alcohol was protected with a TBDPS group. The THP protecting group was removed using bromine and 1,2-bis(diphenylphosphino)ethane, the primary alcohol was converted into a bromide and the remaining compound was treated with NaHMDS and dimethyl phosphite to furnish the key intermediate **254** in 47% yield in 5 steps.



Scheme 7.02: Synthesis of compound **254**.²⁷⁶

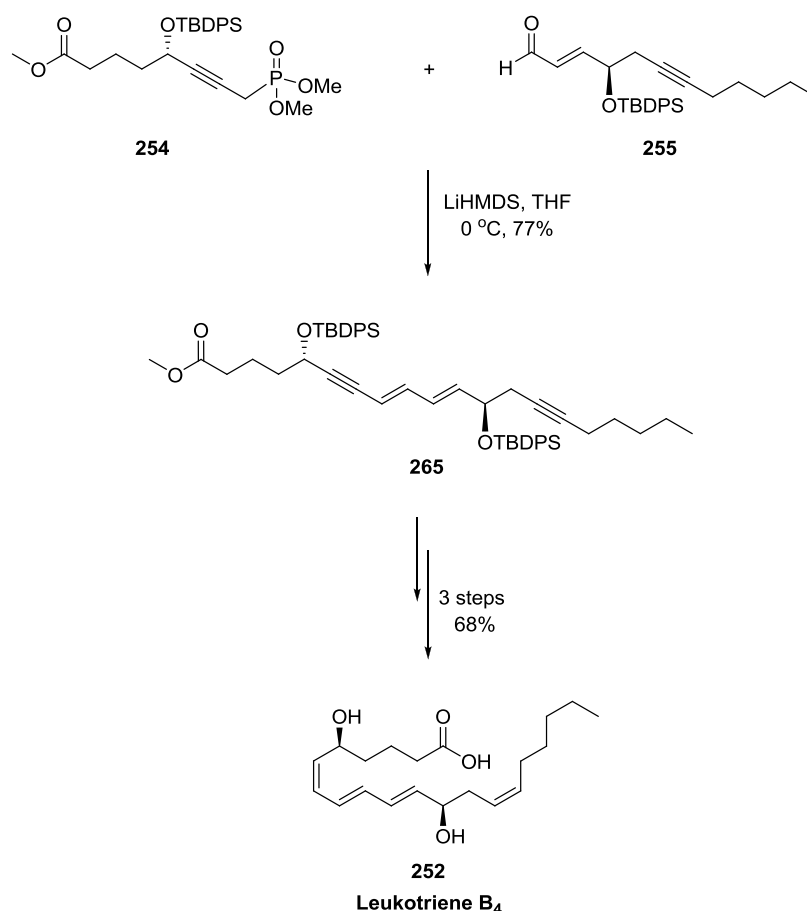
The aldehyde **255** provided access to the C₉–C₂₀ portion of leukotriene B₄. The starting point for this compound was (2*R*)-(-)-glycidol 4-nitrobenzoate **260** (Scheme 7.03). Treatment of **260** with BF₃•OEt₂ and the organolithium reagent **261** led to ring opening of the epoxide. The resulting alcohol was protected with a TBDPS group to afford compound **262** in 85% yield in 2 steps. Hydrolysis of the *p*-nitrobenzoate using LiOH gave a primary alcohol. This was oxidised using TPAP to furnish the aldehyde **263**. Finally, a Wittig olefination with the ylide **264** afforded the key intermediate **255** in 52% yield in 5 steps.



Scheme 7.03: Synthesis of the aldehyde **255**.²⁷⁶

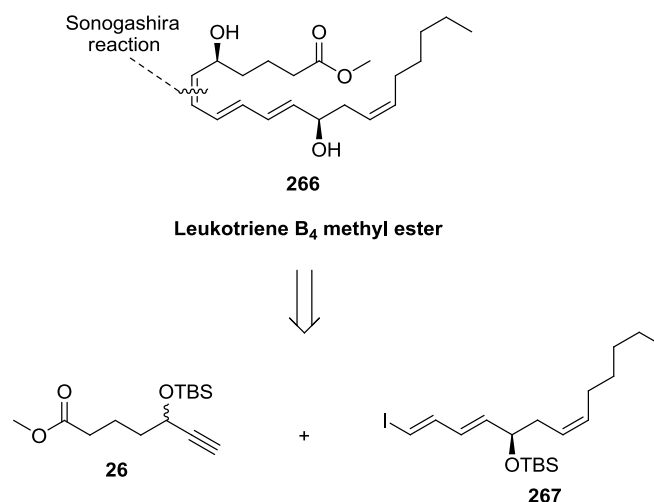
The final steps of the synthesis involved a Horner-Wadsworth-Emmons olefination between compounds **254** and **255** (Scheme 7.04). This gave the *E*-alkene at the

C₈–C₉ position. Leukotriene B₄ was then prepared in 3 steps and 68% yield from compound **265** by global deprotection of the silyl groups, reduction of the C₆–C₇ and C₁₄–C₁₅ alkynes using Lindlar’s catalyst and hydrolysis of the methyl ester.



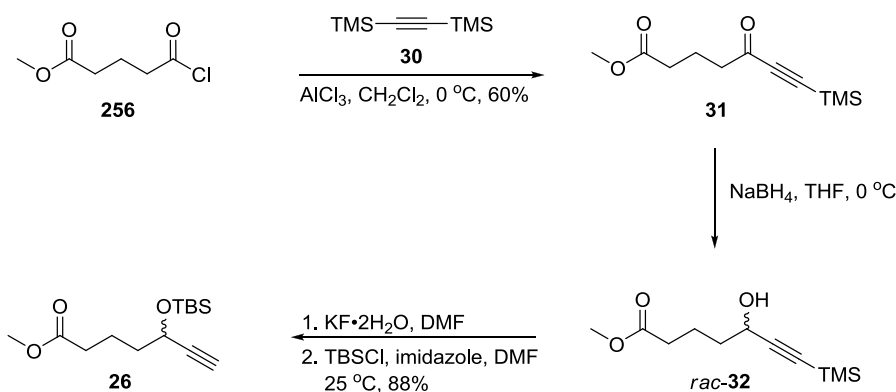
Scheme 7.04: Final steps in the synthesis of leukotriene B₄.²⁷⁶

A cross-coupling strategy has also been used to form the triene portion of leukotriene B₄. This was implemented in four total syntheses.^{277, 280-282} One example of this approach was detailed by Avignon-Tropis and co-workers in the preparation of the leukotriene B₄ methyl ester **266** (Scheme 7.05).²⁷⁷ The key disconnection in the synthesis was a Sonogashira reaction between the alkyne **26** and the iodide **267**.



Scheme 7.05: Retrosynthesis of the leukotriene B₄ methyl ester **266** developed by Avignon-Tropis.²⁷⁷

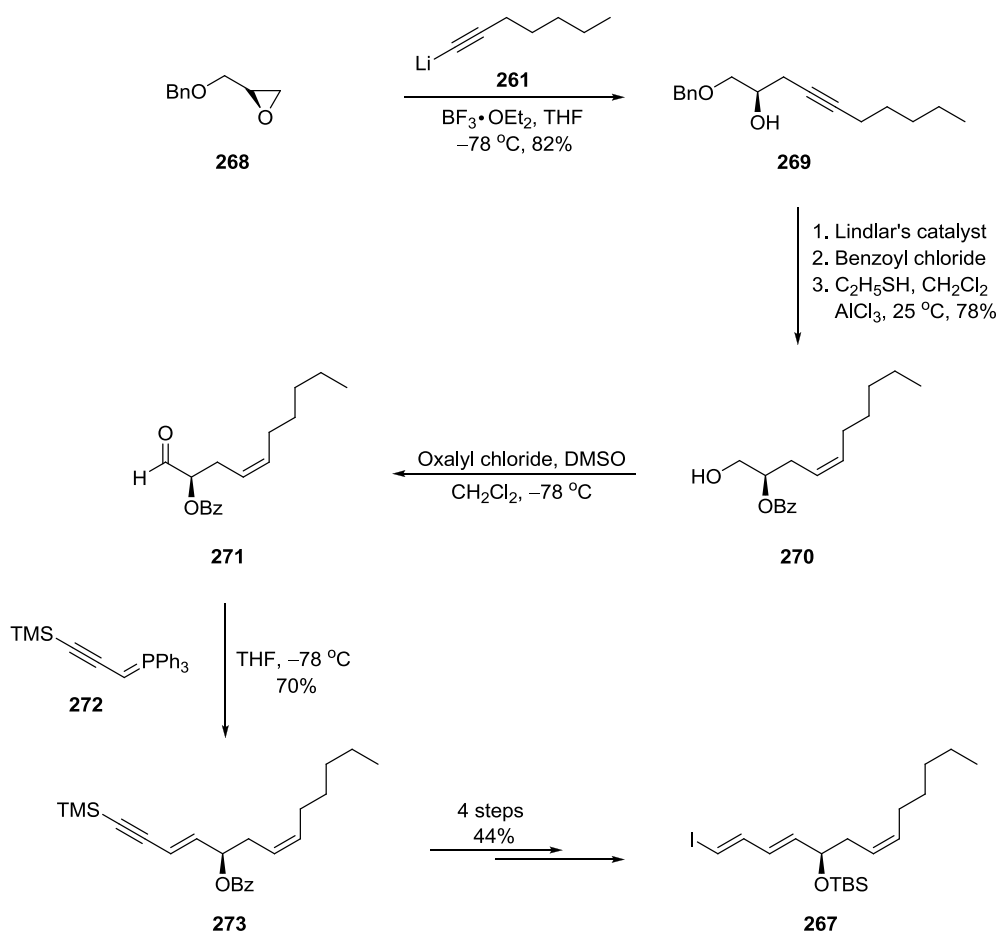
Compound **26** is a common intermediate in four other total syntheses of leukotriene B₄ and was prepared by Petasis and Allard for the total synthesis of resolvins E1.^{180,182} One reason for its widespread use is that it provides access to the C₁-C₅ hydroxyacid portion of the target compound in only 4 steps from methyl 4-chloroformylbutanoate **256**. The synthesis of compound **26** is shown in Scheme 7.06. This is similar to the pathway detailed by Petasis in Scheme 1.03.¹⁸⁰ The main difference was the reduction of the ketoester **31**. In this synthesis, compound **31** was reduced to *rac*-**32** while in the pathway developed by Petasis, the enantiomerically pure (*S*)-alcohol of **32** was prepared using *S*-Alpine-Borane[®].



Scheme 7.06: Synthesis of compound **26**.²⁷⁷

Starting from the benzyl protected glycidol **268**, the key fragment **267** was prepared in 10 steps (Scheme 7.07). Alkylation of **268** with the organolithium reagent **261** furnished compound **269** in 82% yield. The alkyne was selectively reduced to the *Z*-

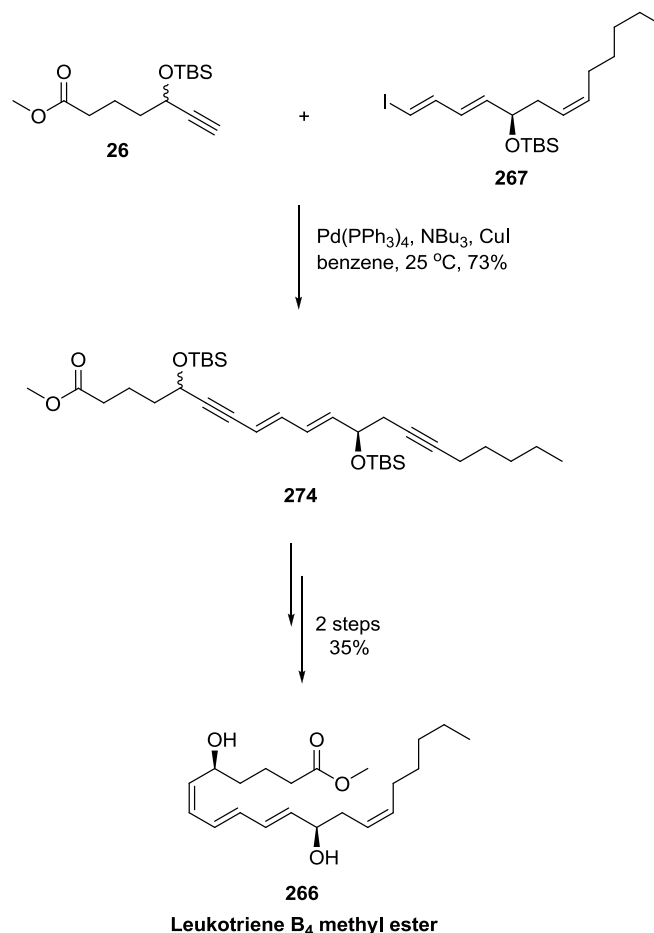
alkene using Lindlar's catalyst, the secondary alcohol was esterified with benzoyl chloride and the benzyl ether was cleaved under acidic conditions to give compound **270** in 78% yield over 3 steps. The resulting alcohol was oxidised using Swern conditions to give the aldehyde **271**. This compound was treated with the ylide **272** to afford compound **273** in 70% yield in 2 steps. Removal of the benzoate ester and TMS group, protection of the allylic alcohol with a TBS group followed by a hydrozirconation reaction using Schwartz's reagent gave compound **267** in 44% yield over 4 steps.



Scheme 7.07: Synthesis of compound **267**.²⁷⁷

The antepenultimate step in the synthesis involved a Sonogashira reaction between the alkyne **26** and the iodide **267** (Scheme 7.08). This afforded compound **274** in 73% yield. The target compound **266** was then prepared in 2 steps from **274** by global deprotection of the silyl groups and reduction of the $\text{C}_6\text{--C}_7$ and $\text{C}_{14}\text{--C}_{15}$ alkynes using a $\text{Zn}(\text{Cu}/\text{Ag})$ amalgam. The resulting diastereoisomers were separated

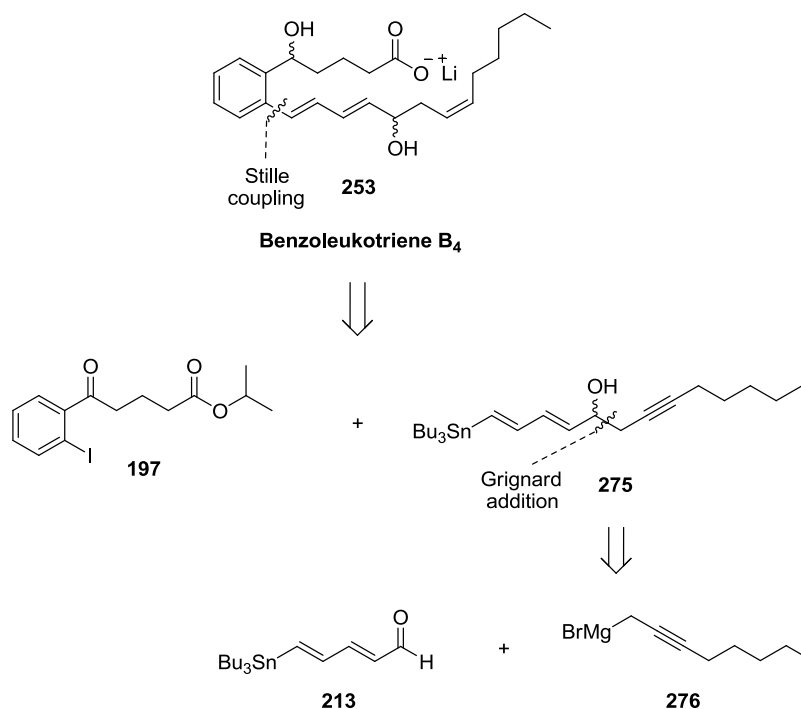
by column chromatography to give the leukotriene B₄ methyl ester **266** in 35% yield from compound **274**.



Scheme 7.08: Final steps in the synthesis of the leukotriene B₄ methyl ester **266**.²⁷⁷

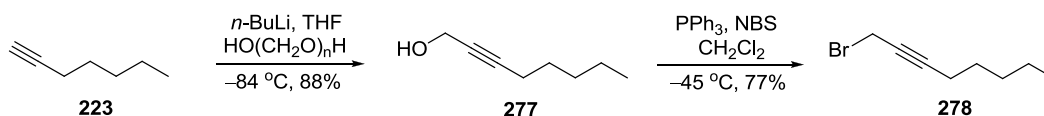
7.3 Retrosynthesis of benzoleukotriene B₄

Benzoleukotriene B₄ could be prepared by a similar strategy to Avignon-Tropis.²⁷⁷ Instead of a Sonogashira reaction, a Stille reaction between the iodide **197** and the stannane **275** could give the benzodiene portion of the target compound (Scheme 7.09). Using the same approach for the preparation of benzo-resolvin E1 (Scheme 4.15), the stannane **275** could be synthesised by the addition of the Grignard **276** to the aldehyde **213**. Having previously synthesised compounds **197** and **213**, attention was focused on the preparation of the Grignard reagent **276**.



Scheme 7.09: Retrosynthesis of benzoleukotriene B₄ **253**.

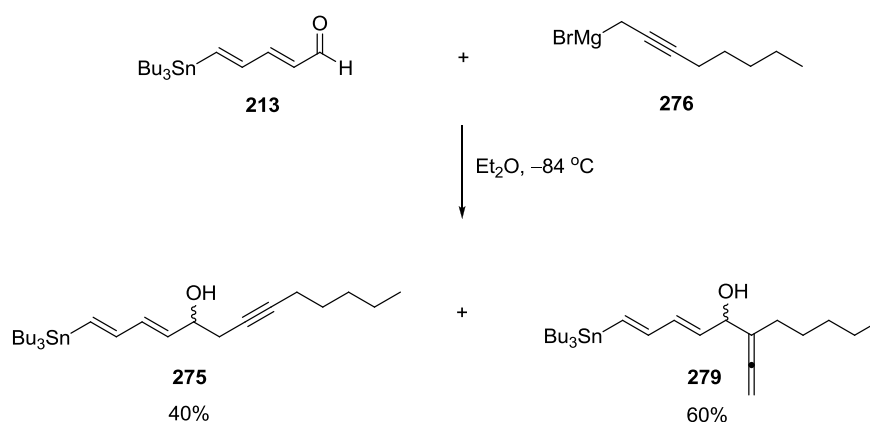
Starting from 1-hexyne, the Grignard reagent **276** was synthesised in 3 steps. Treatment of 1-hexyne **223** with *n*-BuLi gave the lithium acetylide which was added to paraformaldehyde at $-84\text{ }^{\circ}\text{C}$ to afford the alcohol **277** in 88% yield (Scheme 7.10). The product showed an absorbance at 3502 cm^{-1} in the IR spectrum and a broad singlet at 2.89 ppm in the ^1H NMR spectrum that was consistent with the newly formed primary alcohol. The alcohol was then converted into a bromo group via an Appel reaction, giving the bromide **278** in 77% yield. The loss of the alcohol absorbance in the IR spectrum of the crude reaction mixture suggested complete consumption of the starting material. Furthermore, the ^1H NMR spectrum of the product matched the spectroscopic data of compound **278** provided by Zhao.²⁸⁷



Scheme 7.10: Synthesis of the bromide **278**.

The bromide **278** in anhydrous ether at room temperature was treated with a Mg(Hg) amalgam. Using this method, Acharya and co-workers prepared the Grignard **276** in 85% yield.²⁸⁸ After stirring the mixture for 2 hours, the resulting Grignard reagent

was added to a solution of the aldehyde **213** in anhydrous ether at $-84\text{ }^{\circ}\text{C}$ (Scheme 7.11). The reaction was monitored by TLC. Two new spots with similar R_f values compared to the starting material were observed after 15 minutes. The reaction mixture was stirred for a further two and a half hours until the starting material was completely consumed. Analysis of the ^1H NMR spectrum for the crude sample revealed a 0.8:1.2 mixture of two new products tentatively assigned as compounds **275** and **279**. Due to the similar polarities of these compounds, separation by column chromatography proved difficult. However, a small amount of **275** and **279** was isolated and characterised by NMR spectroscopy.



Scheme 7.11: Treatment of compound **213** with the Grignard reagent **276**.

The ^1H NMR spectrum of the desired product **275** showed four vinylic signals in the region of 5.69–6.52 ppm along with three resonances at 1.46–1.51, 1.25–1.44 and 0.93–0.97 ppm due to the stannane functional group. The signal at 2.17 ppm could be assigned to the methylene hydrogens in blue while the signals at 2.46 and 2.41 ppm are ascribed to the propargylic hydrogens shown in red (Figure 7.02). These hydrogens are diastereotopic and gave a complex coupling pattern. The coupling constants of 2.4 and 2.5 Hz were attributed to the propargylic hydrogens (blue) at 2.17 ppm while the coupling constants of 7.0 and 16.4 Hz are indicative of vicinal and geminal coupling respectively.

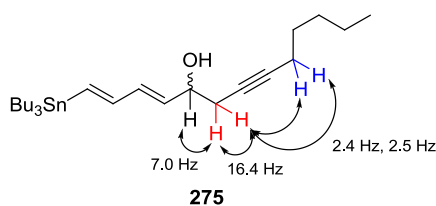


Figure 7.02: Key coupling constants for the stannane **275**.

The other compound in the reaction mixture was tentatively assigned as the allene **279** based on the ^{13}C NMR spectrum. The spectrum showed four signals between 132–146 ppm that could be ascribed to the four vinylic carbons while the resonance at 72.6 ppm could be assigned to the carbon bearing the hydroxyl group. The key signals of interest are at 79.7, 107.5 and 204.2 ppm (Figure 7.03). These are characteristic of a disubstituted allene which is consistent with the structure of compound **279**.

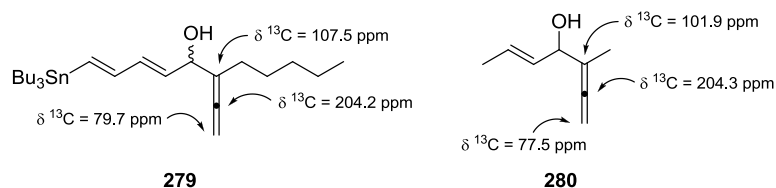
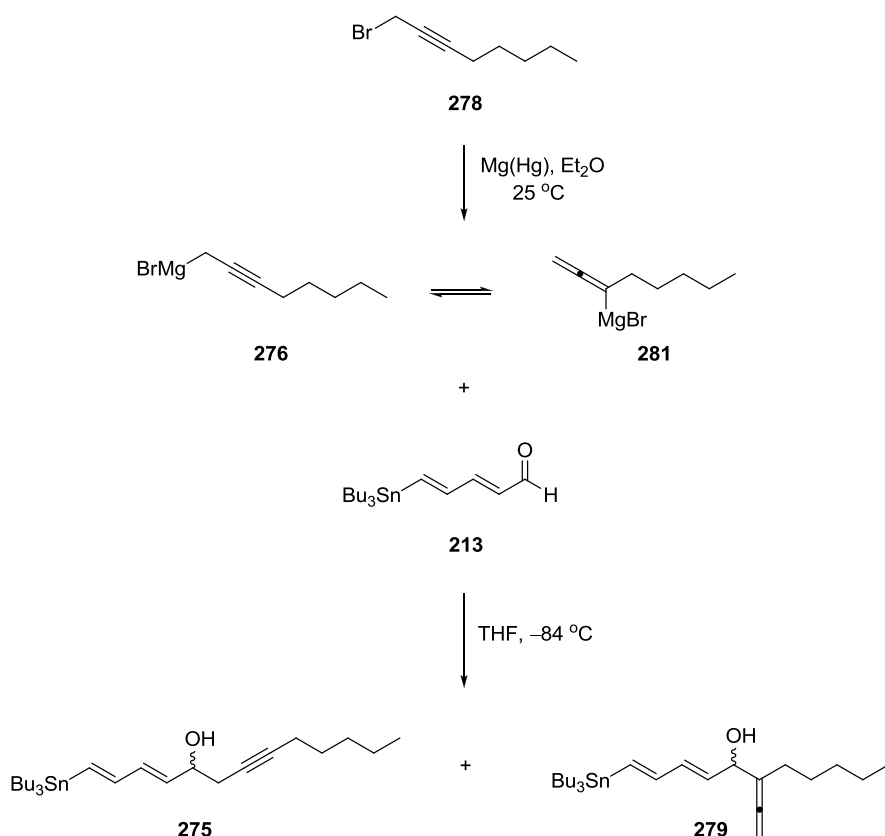


Figure 7.03: A comparison of the key ^{13}C NMR resonances for compounds **279** and **280** in CDCl_3 .

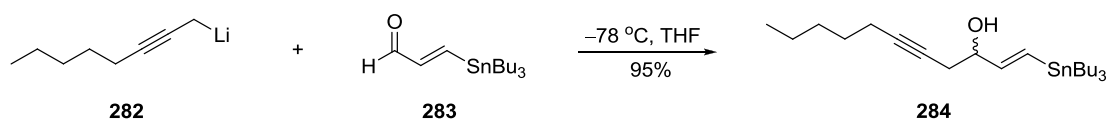
Focusing on the allene functional group, the ^{13}C NMR spectrum of compound **279** is similar to the literature compound **280**.²⁸⁹ As shown in Figure 7.03, the allene signal at 204.2 ppm for compound **279** has a chemical shift similar to the disubstituted allene carbon of **280** which is observed at 204.3 ppm. The ^{13}C NMR spectrum of **279** showed a resonance at 79.7 ppm that could be ascribed to the terminal carbon of the allene. This is similar to the chemical shift at 77.5 ppm reported for compound **280**. The resonance at 107.5 ppm for compound **279** was assigned to the remaining carbon. This is further downfield compared to the signal observed for compound **280**. Despite this disparity, this signal is consistent with examples of other allenes in the literature.²⁹⁰⁻²⁹¹

Rearrangement of the Grignard reagent **276** at room temperature could account for the formation of the allene **279** (Scheme 7.12). Studies by Gaudemar and Yanagisawa suggest that compound **276** is in equilibrium with the Grignard **281**.²⁹²⁻²⁹³ In an attempt to suppress the formation of **281**, compound **278** was treated with a $\text{Mg}(\text{Hg})$ amalgam at a cooler temperature of 0°C followed by the addition of the aldehyde **213** at -84°C . The ^1H NMR spectrum of the crude reaction mixture showed an improvement in the yield of the stannane **275**, with a 1:1 mixture of **275** and **279** observed when the Grignard initiation was maintained at 0°C .



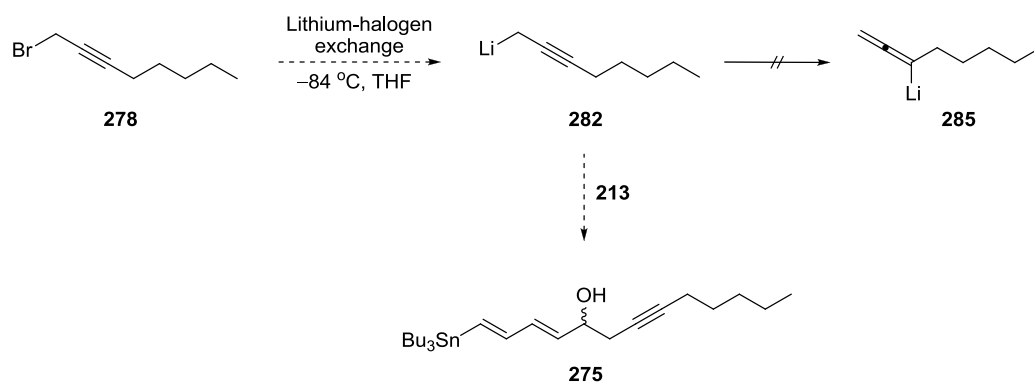
Scheme 7.12: Equilibration of the Grignard reagent **276** with the allene **281**.

In light of this result, the reaction was repeated using an organolithium reagent. Unlike the Grignard **276**, an organolithium reagent could be prepared at cryogenic temperatures. Oda and co-workers have shown that at $-78\text{ }^\circ\text{C}$, compound **282** does not form allenic products in a similar reaction.²⁹⁴ For example, addition of this compound to the aldehyde **283** gave the stannane **284** in 95% yield without affording the allene isomer (Scheme 7.13).



Scheme 7.13: Addition of the organolithium reagent **282** to the aldehyde **283**.²⁹⁴

To emulate these results, a lithium-halogen exchange between *n*-BuLi and compound **278** at $-84\text{ }^\circ\text{C}$ was planned to give the organolithium reagent **282** (Scheme 7.14). This compound could be treated with the aldehyde **213** to afford the stannane **275** as the sole product.

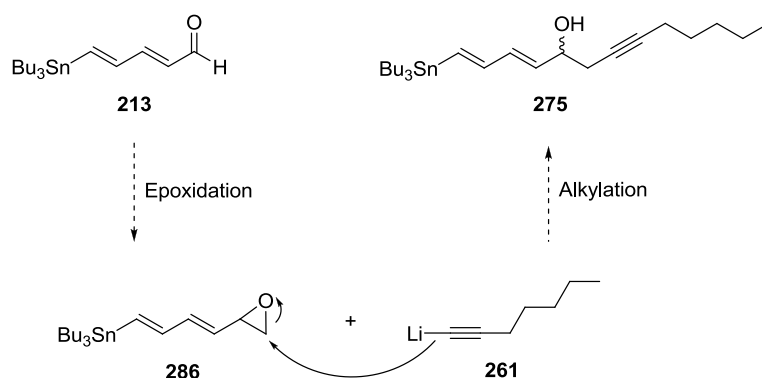


Scheme 7.14: Planned synthesis of the stannane **275** via a lithium-halogen exchange.

Adapting the procedure described by Rajagopalan and Zweifel,²⁹⁵ compound **278** in anhydrous tetrahydrofuran was treated with one equivalent of $n\text{-BuLi}$ at $-84\text{ }^{\circ}\text{C}$. The reaction mixture was stirred at this temperature for 6 hours. One equivalent of the aldehyde **213** in anhydrous tetrahydrofuran was then added and the mixture was stirred for a further 6 hours at $-84\text{ }^{\circ}\text{C}$. Disappointingly, the ^1H NMR spectrum of the crude sample showed no improvement in the yield of **275**, with a 1:1 mixture of compounds **275** and **279** observed.

7.4 Epoxidation strategy

A new two step strategy to synthesise the stannane **275** was implemented to overcome the rearrangement of the organolithium reagent **282** (Scheme 7.15). Converting the aldehyde to an epoxide followed by alkylation at the terminal position could give the stannane **275**. This pathway would eliminate the need to form propargylic Grignard or organolithium reagents such as compounds **276** and **282** that readily equilibrate.

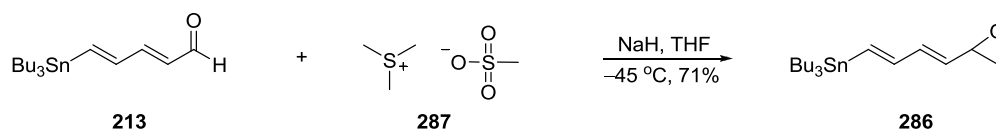


Scheme 7.15: Alternate pathway to prepare the stannane **275**.

Epoxidation of compound **213** could be achieved via a Corey-Chaykovsky reaction. This involves the addition of a sulfur ylide to an aldehyde to afford a terminal epoxide. The conditions are mild and the reaction gives good yields of the desired epoxide.²⁹⁶ A common sulfur ylide used in these reactions is dimethylsulfonium ylide. This ylide is easily formed by treating dimethylsulfonium iodide with a base such as NaH.²⁹⁷ Alternatively, trimethylsulfonium methanesulfonate **287** could be used as a viable substitute.²⁹⁸ Following the procedure developed by Travers,²⁹⁹ compound **287** was synthesised from DMSO.

Adapting the procedure by Kavanagh and co-workers,²⁹⁷ trimethylsulfonium methanesulfonate **287** in anhydrous tetrahydrofuran was treated with NaH at 0 °C to form the sulfur ylide (Scheme 7.16). This was added dropwise to a solution of the aldehyde **213** in anhydrous tetrahydrofuran at -45 °C. After 4 hours at this temperature, complete consumption of the starting material was observed and the formation of a new spot by TLC was noted. This compound was identified as the epoxide **286** and was isolated in 71% yield. The driving force for this reaction was

the formation a sulfonium cation intermediate that readily eliminates dimethyl sulfide to afford the epoxide **286**.



Scheme 7.16: Preparation of the epoxide **286**.

The ^1H NMR spectrum of the product showed the appearance of three new resonances at 3.36, 2.99 and 2.68 ppm that were ascribed to the three diastereotopic hydrogens of the newly formed epoxide (Figure 7.04). Four resonances between 5.30–6.53 ppm were also observed in the ^1H NMR spectrum. These were assigned to the four vinylic hydrogens. The ^{13}C NMR spectrum of the product also showed two new signals at 52.4 and 49.4 ppm that are consistent with the methine and methylene signals of the epoxide.

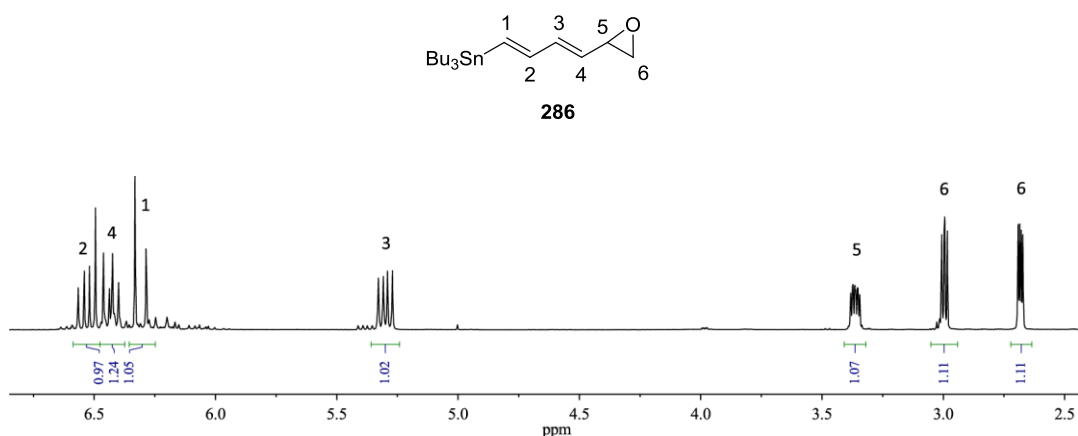
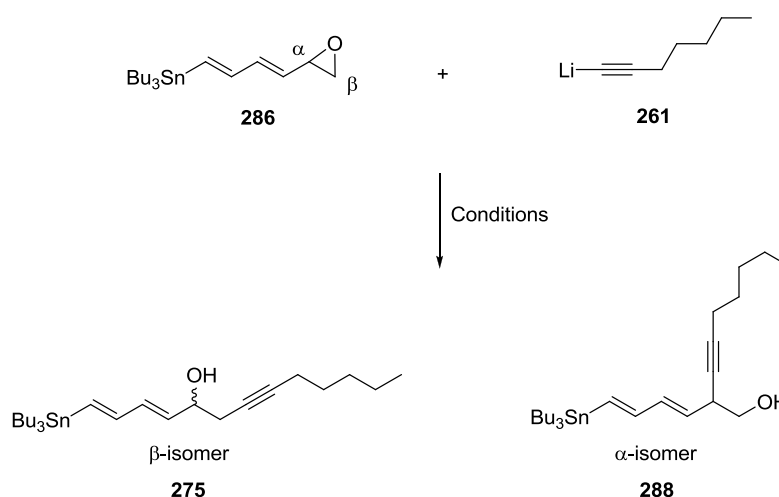


Figure 7.04: ^1H NMR spectrum of the epoxide **286** in CDCl_3 (2.50–6.75 ppm).

With the epoxide **286** in hand, the alkynylation step was investigated. Alkynylation of the epoxide could proceed at either the α or β -position (Table 7.01). This would give a mixture of the regioisomers **275** and **288**. To direct the addition of the organolithium acetylide **261** to the unhindered β -position, the reaction mixture was cooled to $-84\text{ }^\circ\text{C}$ (Table 7.01, entry 1). No new products were observed after stirring the mixture for 2 hours, as judged by TLC. Warming the reaction mixture to $0\text{ }^\circ\text{C}$ also gave the same result, with the starting material recovered in quantitative yields (Table 7.01, entry 2).

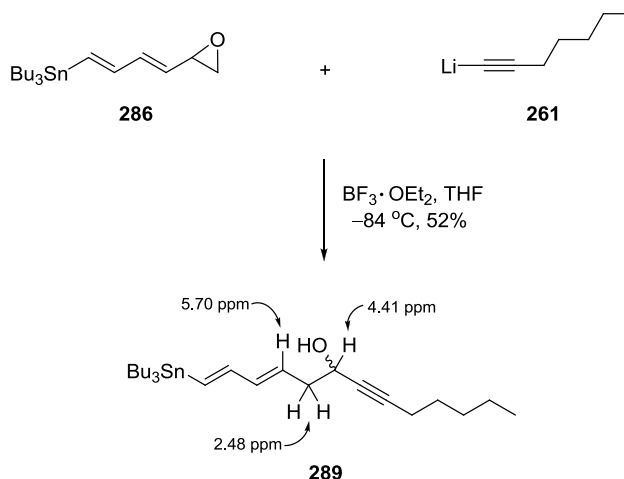
This result prompted the use of a mild Lewis acid such as lithium perchlorate. Chini and co-workers have shown that lithium perchlorate can direct the alkynylation of terminal epoxides towards the β -position, giving β -substituted products in greater than 95% yield.³⁰⁰ Following the conditions outlined by Chini,³⁰⁰ two equivalents of lithium perchlorate were added to a mixture of the epoxide **286** and the organolithium acetylide **261** in anhydrous tetrahydrofuran at 0 °C (Table 7.01, entry 3). The reaction was monitored over 24 hours. Only starting material was recovered from the crude mixture after this time. Likewise, no reaction was observed when anhydrous cerium chloride was used (Table 7.01, entry 4).

Table 7.01: Attempted alkynylation of the epoxide **286**.



Entry	Conditions	Result
1	286 (1 eq.), 261 (1 eq.), THF, -84 °C, 2 hrs	no reaction
2	286 (1 eq.), 261 (1 eq.), THF, 0 °C, 6 hrs	no reaction
3	286 (1 eq.), 261 (1 eq.), LiClO ₄ (2 eq.), THF, 0 °C, 24 hrs	no reaction
4	286 (1 eq.), 261 (1 eq.), CeCl ₃ (2 eq.), THF, 0 °C, 24 hrs	no reaction

When a stronger Lewis acid such as BF₃•OEt₂ was used, the starting material was completely consumed after 30 minutes. A new compound with the same R_f value as the stannane **275** was observed. This compound was isolated in 52% yield and was tentatively assigned as the alcohol **289** (Scheme 7.17).



Scheme 7.17: $\text{BF}_3 \cdot \text{OEt}_2$ mediated alkylation of the epoxide **286**.

The ^1H NMR and ^{13}C NMR spectra of the product are similar but not identical to the spectra of the stannane **275** (Figure 7.05). The ^1H NMR spectrum showed four signals between 5.70–6.52 ppm that are ascribed to the four vinylic hydrogens of the alcohol **289**. The diagnostic vinylic signal is at 5.70 ppm. This is an apparent doublet of triplets which is different to the doublet of doublet multiplicity observed for the same vinylic signal of the stannane **275**. The ^1H NMR spectrum of the product also showed two resonances at 2.48 and 2.12 ppm that are attributed to two sets of methylene hydrogens. These have different chemical shifts to the stannane **275** where the methylene resonances adjacent to the alkyne are at 2.46, 2.41 and 2.17 ppm. The coupling pattern for these signals is also different. The resonance at 2.48 ppm is an apparent triplet while the propargylic signals at 2.46 and 2.41 ppm of the stannane **275** have a more complex multiplicity. A 2D-COSY experiment of the product showed a correlation between the vinylic signal at 5.70 ppm and the methylene resonance at 2.48 ppm. In contrast, the stannane **275** showed no correlation between the vinylic signal at 5.69 ppm and the propargylic resonances at 2.46 and 2.41 ppm. The ^{13}C NMR spectrum of the product was also different to the spectrum of compound **275**. The signal of interest was the carbon bearing the alcohol. This was observed at 62.3 ppm for the product and 70.8 ppm for the stannane **275** (Figure 7.05).

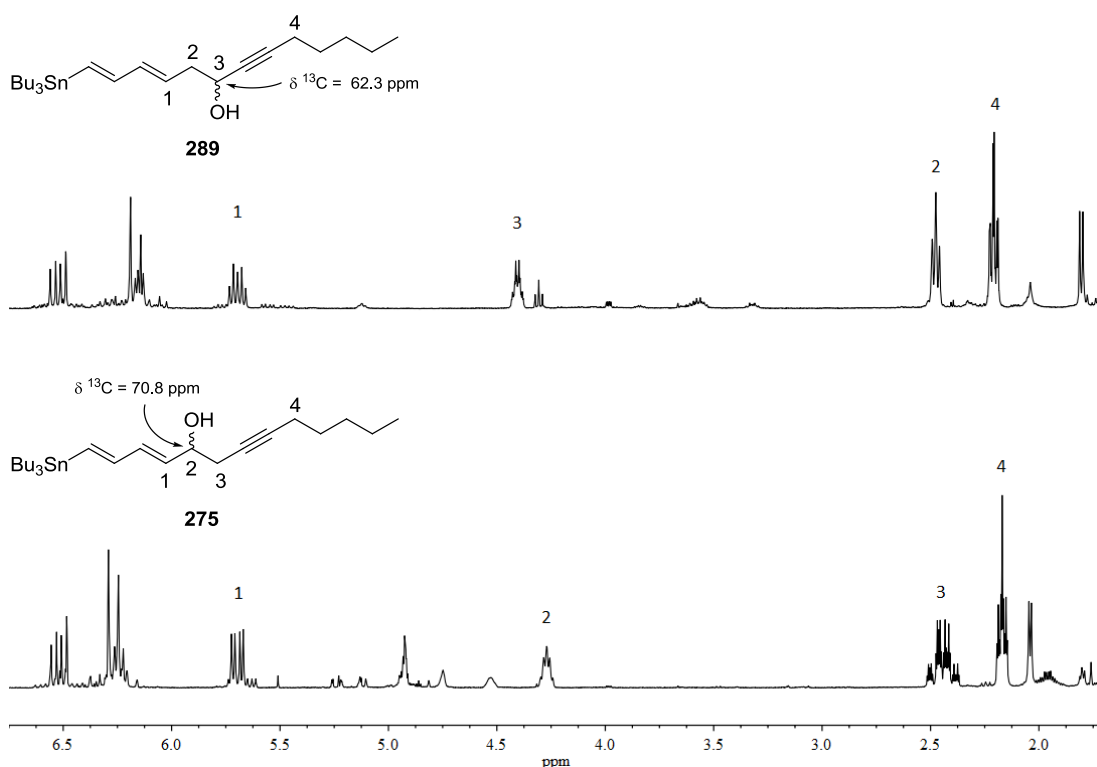
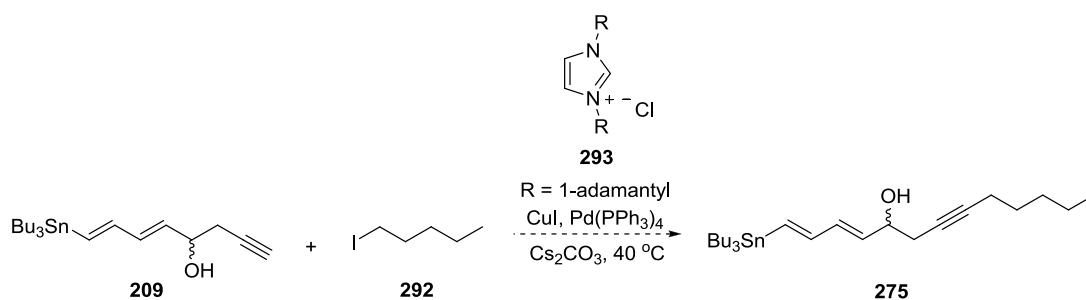


Figure 7.05: Key ^1H NMR signals for compounds **289** and **275** in CDCl_3 (2.20–6.60 ppm).

The proposed mechanism in Scheme 7.18 could account for the synthesis of the alcohol **289**. $\text{BF}_3 \cdot \text{OEt}_2$ was able to mediate the ring opening of the epoxide **286**. This led to the formation of the resonance stabilised allylic carbocation **290** which was more favourable than the primary carbocation. A 1,2-hydride shift gave the aldehyde **291**, followed by the 1,2-addition of the organolithium reagent **261**. Finally, a hydrolytic workup afforded the alcohol **289**.

unsuccessful. To circumvent the problems encountered in this chapter, the stannane **275** could be prepared via a Sonogashira reaction between compound **209** and 1-iodopentane **292** (Scheme 7.20). Sp^3 -hybridised alkyl iodides are unfavourable substrates for the Sonogashira reaction as they readily undergo β -hydride elimination, giving undesirable alkene side-products.³⁰² However, studies by Eckhardt and Fu have shown that carbene additives such as compound **293** can suppress β -hydride elimination, affording high yields of the Sonogashira products.³⁰² This method could be investigated in the future to prepare the stannane **275**.



Scheme 7.20: Preparation of the stannane **275** via a Sonogashira approach.

Chapter 8

Conclusions

Resolvin E1 is a short-lived anti-inflammatory lipid mediator. One of its proposed modes of degradation is isomerisation of the 6Z-alkene.¹⁷² This gives the 6E-isomer that is no longer anti-inflammatory.¹⁷⁷ To inhibit this pathway, a benzene fused analogue of resolvin E1 was targeted (Figure 8.01). This was named benzo-resolvin E1. The inclusion of the benzene ring at the C₆–C₇ position would improve the chemical stability of resolvin E1 by inhibiting the isomerisation pathway.

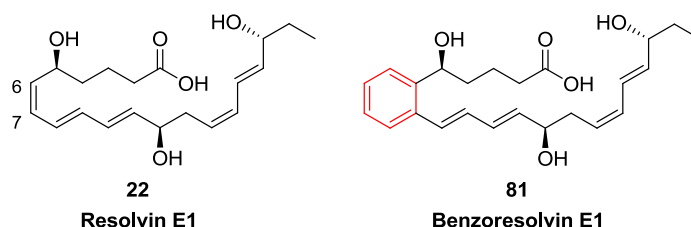
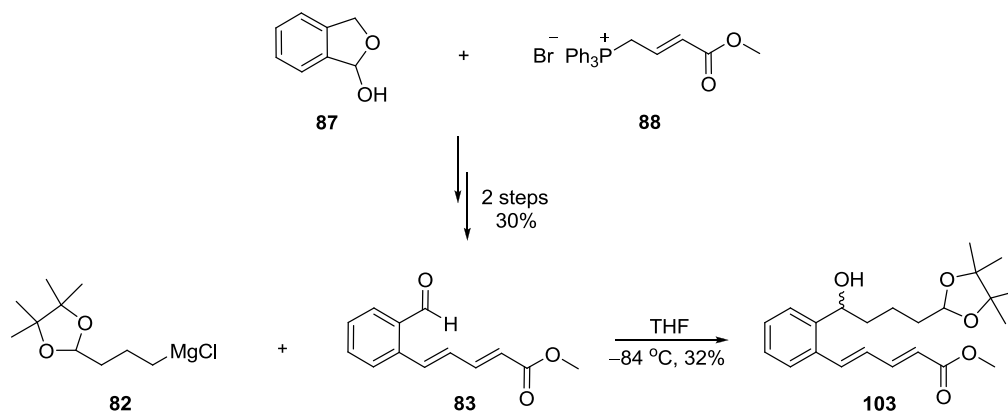


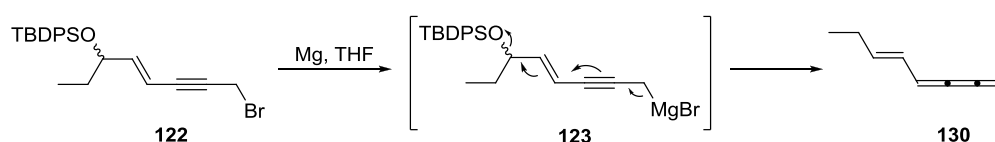
Figure 8.01: Resolvin E1 and benzo-resolvin E1.

The initial synthetic pathway involved a Wittig reaction between the lactol **87** and the ylide of compound **88** followed by addition of the Grignard reagent **82** to afford the benzodiene and the C₁–C₅ hydroxyacid portion of the target compound (Chapter 1). Both reactions gave low yields of their respective products, the ester **83** and compound **103** (Scheme 8.01).



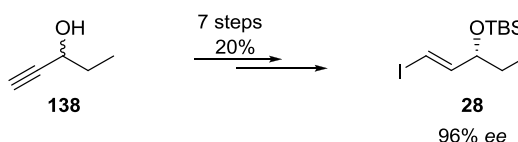
Scheme 8.01: Preparation of the key intermediate **103**.

To prepare the C₁₃–C₂₀ portion of the target compound, propargyl alcohol was used as the starting material (Chapter 1). From this compound, the bromide **122** was synthesised in 4% yield in 8 steps. Compound **122** could be converted into the Grignard reagent **123** and added to the aldehyde **86** to give the key intermediate **85** which is 3 steps from the target compound. Unfortunately, when the bromide **122** was treated with magnesium turnings at 0 °C, decomposition of the reaction mixture was observed. A possible mode of degradation was the elimination of TBDPSOMgBr to give the highly reactive cumulene **130** (Scheme 8.02). Attempts to mitigate this rearrangement by cooling the reaction mixture to –84 °C upon Grignard initiation were unsuccessful.



Scheme 8.02: Proposed mode of degradation for the Grignard reagent **123**.

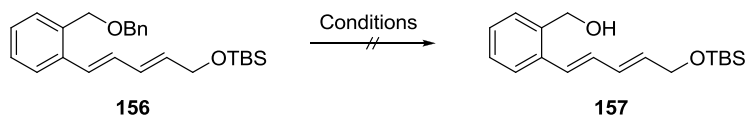
In view of this, the Grignard reagent **123** was segmented into two smaller compounds, propargylmagnesium bromide and the iodide **28**. This would circumvent the rearrangement observed in Scheme 8.02. A new pathway was developed for the synthesis of the iodide **28** (Scheme 8.03). Starting from 1-pentyn-3-ol, compound **28** was prepared in 20% yield and 96% *ee* in 7 steps (Chapter 3). This was comparable to the yield reported in the literature.²¹¹ A scalable pathway for this compound was also developed using propionaldehyde and 2-methyl-3-butyn-2-ol. These compounds are cheap, making large quantities of the iodide **28** achievable.



Scheme 8.03: Preparation of the iodide **28** from 1-pentyn-3-ol.

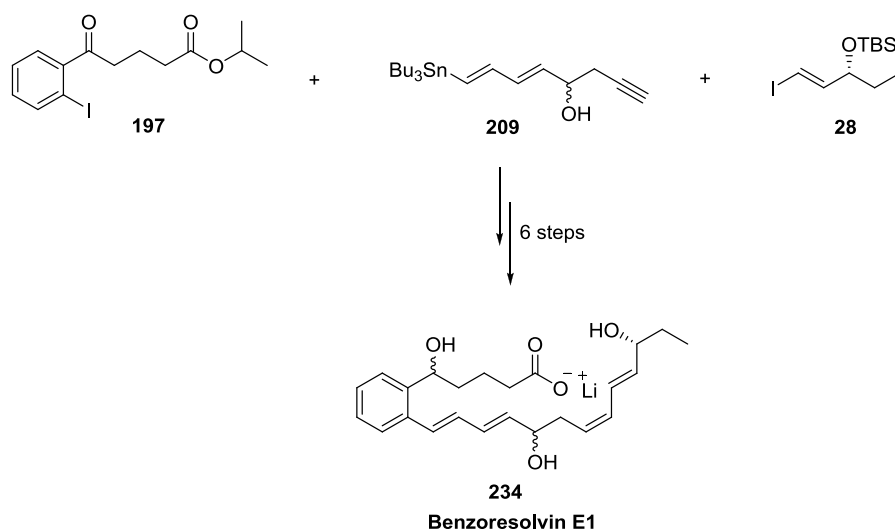
With the iodide **28** in hand, the Wittig reaction between the lactol **87** and the ylide of compound **88** was revisited. By protecting the alcohol of **91** with a benzyl group, the Wittig product was furnished in 64% yield (Chapter 3). This was higher than the yield for compound **83** (30%). Using the model compound **156**, a range of conditions

and reagents were tested to remove the benzyl group (Scheme 8.04). These led to either degradation or deprotection of the allylic alcohol. A similar result was observed when PMB was used as the protecting group (Chapter 3). In light of these shortcomings, a new protecting group free synthesis of benzoeresolvin E1 was planned (Chapter 4).



Scheme 8.04: Unsuccessful removal of the benzyl protecting group.

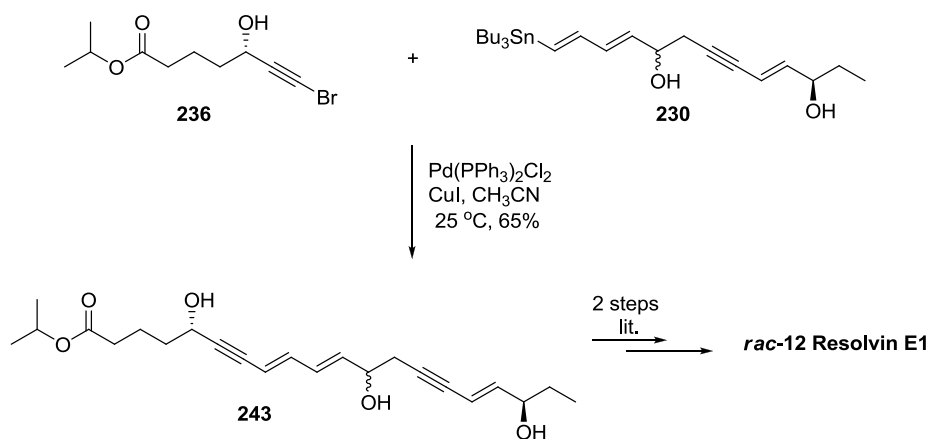
This synthetic route utilised a sequential Sonogashira-Stille reaction between compounds **197**, **209** and **28** (Scheme 8.05). From these compounds, the lithium carboxylate salt of benzoeresolvin E1 was prepared in 6 steps. The synthesis of this compound had the longest linear sequence of 13 steps from 1-pentyn-3-ol **138**, with an overall yield of 2%. The key fragment in the synthesis was the alcohol **209**. This compound has two handles, a terminal alkyne and a stannane moiety. Using the iodide **196** as a model compound, the alkyne was shown to be more reactive than the stannane. This difference in reactivity was exploited to couple the alcohol **209** with the iodide **28**, giving the Sonogashira product **226** as the sole product. Subsequent deprotection of the alcohol followed by a Stille reaction with compound **197** afforded the key intermediate **231**. Using this strategy, the benzodiene and enyne portions of the target compound were prepared in only 3 steps.



Scheme 8.05: Synthesis of the lithium carboxylate salt of benzoeresolvin E1 **234**.

Having synthesised benzoiresolvin E1, the chemical stability of this compound was investigated. A ^1H NMR study conducted at room temperature showed no change to the target compound over 4 days. In comparison to the study by Maddapati and Zhou,¹⁹⁵ resolvin E1 was shown to degrade over the same period of time. This suggests that the benzene ring was significant in improving the stability of resolvin E1 (Chapter 4). *In vitro* studies also showed benzoiresolvin E1 binds to the BLT-1 receptor with an inhibitory constant of 1.05 μM . This is comparable to the BLT-1 antagonist SC-41930 that has a K_i of 1.00 μM ²⁶⁹ but is higher than the inhibitory constant of resolvin E1 ($K_i = 70$ nM),¹⁸⁶ inferring that the fused benzene ring weakens but retains the binding towards the BLT-1 receptor.

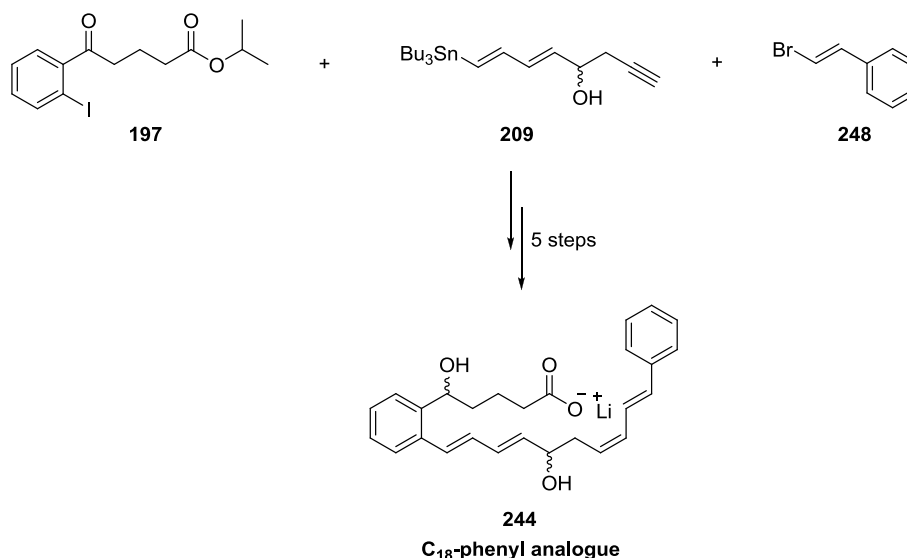
Using the same convergent strategy, the formal total synthesis of *rac*-12 resolvin E1 was completed (Chapter 5). The key fragment in this pathway was the bromide **236**. This compound was furnished in 91% *ee* and 7% yield in 7 steps. The linchpin of the synthesis was a Stille reaction between this compound and the stannane **230** (Scheme 8.06). This allowed access to the enyne portion of resolvin E1 in only one step. The product of this reaction intersects the total synthesis of resolvin E1 developed by Allard and was only 2 steps from the target compound.¹⁸²



Scheme 8.06: Formal total synthesis of *rac*-12 resolvin E1.

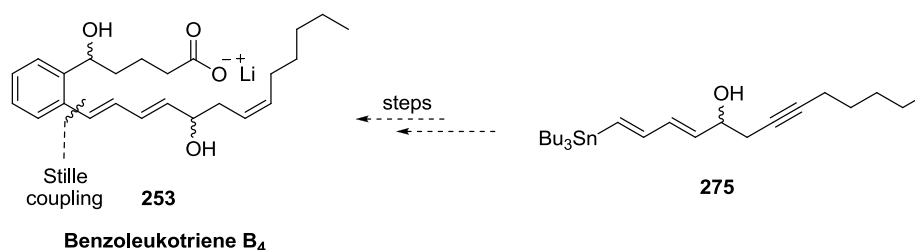
Using the Sonogashira-Stille coupling strategy, a C_{18} -phenyl substituted analogue of benzoiresolvin E1 was prepared (Chapter 6). This compound was synthesised in 5 steps from compounds **197**, **209** and **248** (Scheme 8.07). *In vitro* studies showed the phenyl analogue **244** binds to the BLT-1 receptor with 68% activity at 10 μM . This is only slightly lower than the activity of benzoiresolvin E1 (76%), suggesting

that the C₁₈-phenyl substituent does not significantly reduce the binding affinity of the molecule.



Scheme 8.07: Synthesis of the C₁₈-phenyl analogue **244**.

Significant advances were made towards the synthesis of a benzene annulated analogue of leukotriene B₄ (Chapter 7). Using the strategy developed for benzo-resolvin E1, the key intermediate **275** was furnished with the allene **279** (Scheme 8.08). As these compounds were difficult to separate via column chromatography, a new two step method was devised. The epoxide **286** in this pathway was prepared in 71% yield using a Corey-Chaykovsky reaction. This compound was difficult to alkylate, with a range of conditions giving the stannane isomer **289** or recovered starting material. Future efforts to prepare compound **275** could utilise a carbene additive to promote the Sonogashira reaction between 1-iodopentane **292** and the alcohol **209**.³⁰²



Scheme 8.08: Proposed synthesis of benzoleukotriene B₄ **253** from the stannane **275**.

Chapter 9

Experimental

9.1 General Procedure

9.1.1 Reactions

Anhydrous diethyl ether and tetrahydrofuran were freshly distilled from sodium/benzophenone under nitrogen. Anhydrous dichloromethane, toluene, ethanol, isopropyl alcohol, *N,N*-dimethylformamide and acetonitrile were freshly distilled from calcium hydride under nitrogen. Anhydrous acetone was freshly distilled from boric anhydride. Degassed solvents were prepared by the freeze-pump-thaw technique. The reaction conditions of 0 °C, -17 °C, -28 °C, -45 °C and -84 °C refer to an ice, an ammonium chloride-ice, a sodium bromide-ice, a liquid nitrogen-acetonitrile and a liquid nitrogen-ethyl acetate bath, respectively. Unless otherwise stated, all reactions were conducted in an atmosphere of nitrogen and the solvents used were anhydrous. All organic extracts were dried with anhydrous potassium carbonate, unless otherwise stated and filtered prior to removal of the solvent under reduced pressure.

9.1.2 Purification of compounds

Column chromatography was performed using Davisil[®] silica gel, whilst radial chromatography was conducted using a Chromatotron Model 7924T (Harrison Research, Palo Alto, California) with Merck silica gel, PF₂₅₄ visualising radial plates. In both chromatographic techniques, increasing proportions of ethyl acetate in light petroleum spirits were used as eluting solvents. Light petroleum refers to hydrocarbon fractions with boiling points between 40–60 °C. For acid-sensitive compounds, the silica gel was treated with 1% triethylamine in petroleum spirits. This is referred to as column conditioning. Fractions were monitored by TLC, with samples run on Merck alumina backed silica gel 60 F₂₅₄ sheets. Compounds were visualised using ultraviolet light and then developed with a potassium permanganate stain containing 1.5 g of KMnO₄, 10 g of K₂CO₃ and 10% NaOH in deionised water.

9.1.3 Characterisation of compounds

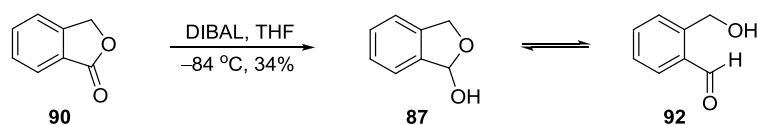
Melting points were determined using a Barnstead Electrothermal 9100 melting point apparatus. NMR spectra were processed on an Ultrashield Bruker 400 spectrometer and were conducted at 298 K. All ^1H NMR spectra were recorded at a frequency of 400 MHz while all ^{13}C NMR spectra were recorded at a frequency of 100 MHz. The resonances for the latter were assigned via ^{13}C -DEPT NMR experiments. Chemical shifts were reported in ppm and the reference signals for CDCl_3 were calibrated to 7.26 ppm and 77.16 ppm for the ^1H NMR and ^{13}C NMR spectra respectively. Infrared spectra were obtained on a Perkin Elmer FT-IR Spectrometer 100 using an attenuated total reflectance attachment with a universal single-bounce diamond-zinc selenide crystal ATR sampling accessory. High resolution electrospray ionisation (ESI) and atmospheric solids analysis probe (ASAP) ionisation accurate mass measurements (HRMS) were recorded in positive mode on a Waters Xevo Q-TOF (quadrupole-Time of Flight) instrument and were conducted by Dr Celine Kelso of the Department of Chemistry, University of Wollongong. Elemental analyses were performed by Robert Herman of the Department of Chemistry, Curtin University. Optical rotations were performed on a Rudolph Research Analytical Autopol I Polarimeter. Enantiomeric excesses were determined by chiral HPLC and were carried out by Dr Thanh Vinh Nguyen at the Research School of Chemistry, Australian National University. The UV spectra of benzo-resolvin E1 and the C_{18} -phenyl analogue were recorded at room temperature using a Perkin Elmer Lambda 35 UV/Vis spectrometer.

9.1.4 Biological testing

Radio-ligand binding assays were investigated to determine the activity of benzo-resolvin E1 and the C_{18} -phenyl analogue towards the BLT-1 receptor. These were carried out by Eurofins Panlabs in Taiwan following the method developed by Winkler.²⁶⁶

9.2 Chapter 2 experimental procedures

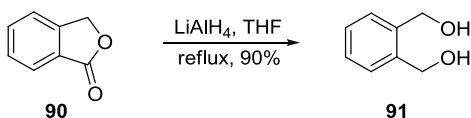
9.2.1 Synthesis of the lactol **87**



Following the procedure by Mikami and Ohmura,¹⁹⁸ DIBAL (1 M in toluene, 8.20 mL, 8.20 mmol, 1.1 eq.) was added dropwise to a solution of phthalide (1.00 g, 7.46 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (30 mL) at $-84\text{ }^{\circ}\text{C}$. The solution was stirred for two and a half hours while maintaining the temperature. The reaction was then quenched upon addition of a saturated aqueous solution of sodium sulfate (20 mL) and the suspension removed by filtration. The organic layer was removed under reduced pressure to afford a yellow liquid. The liquid was subjected to column chromatography. Elution with 70% ethyl acetate/light petroleum afforded a mixture of the lactol **87** and the aldehyde **92** (34:16) as a yellow liquid (345 mg, 34%). The spectroscopic data matched that reported by Makami and Ohmura.¹⁹⁸

¹H NMR (400 MHz, CDCl₃): δ 10.09 (1 H, s, aldehyde), 7.87 (1 H, m, aldehyde), 7.29–7.61 (7 H, m, lactol/aldehyde), 6.48 (1 H, br. s, lactol), 5.28 (1 H, s, lactol), 5.00 (1 H, d, $J = 12.8\text{ Hz}$, lactol), 4.83 (1 H, s, lactol), 4.21 (1 H, br. s, aldehyde), 3.41 (2 H, s, aldehyde) ppm.

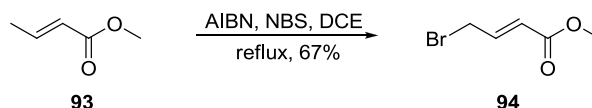
9.2.2 Preparation of the diol **91**



LiAlH₄ (4.13 g, 0.11 mol, 1.6 eq.) at $0\text{ }^{\circ}\text{C}$ was added in portions to a solution of phthalide (9.12 g, 0.07 mol, 1.0 eq.) in anhydrous tetrahydrofuran (240 mL). The reaction mixture was heated under reflux for 5 hours. The mixture was cooled to $0\text{ }^{\circ}\text{C}$ and quenched with deionised water (30 mL). The reaction mixture was filtered and the filtrate concentrated under reduced pressure to afford the diol **91** as a white solid (8.45 g, 90%); m.p. $64\text{--}65\text{ }^{\circ}\text{C}$ (lit. m.p. $62\text{--}63\text{ }^{\circ}\text{C}$).³⁰³ The spectroscopic data matched that reported in the literature.³⁰³

¹H NMR (400 MHz, DMSO): δ 7.38 (2 H, m), 7.21 (2 H, m), 5.05 (2 H, t, J = 5.5 Hz), 4.54 (4 H, d, J = 5.5 Hz) ppm.

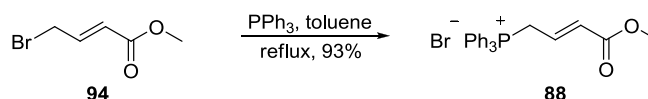
9.2.3 Bromination of methyl crotonate



Following the procedure outlined by Baeckström and co-workers,³⁰⁴ a mixture of AIBN (328 mg, 2.00 mmol, 1 mol%), *N*-bromosuccinimide (24.89 g, 0.14 mol, 0.7 eq.) and methyl crotonate (20.00 g, 0.20 mol, 1.0 eq.) in dichloroethane (100 mL) was heated under reflux for 16 hours. The mixture was cooled to room temperature and concentrated under reduced pressure to afford a yellow liquid. The liquid was subjected to column chromatography. Elution with 10% ethyl acetate/light petroleum gave compound **94** as a colourless oil (23.96 g, 67%). The spectroscopic data matched that reported in the literature.³⁰⁴

¹H NMR (400 MHz, CDCl₃): δ 6.84 (1 H, m), 5.89 (1 H, d, J = 15.4 Hz), 3.90 (2 H, d, J = 7.4 Hz), 3.58 (3 H, s) ppm.

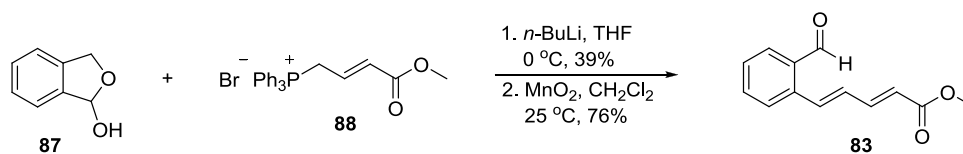
9.2.4 Preparation of the phosphonium salt **88**



Adapting the procedure from Graden and co-workers,³⁰⁵ a solution of the bromide **94** (2.67 g, 14.92 mmol, 1.0 eq.) and triphenylphosphine (3.91 g, 14.92 mmol, 1.0 eq.) in toluene (30 mL) was heated under reflux for 2 hours. The reaction mixture was filtered and the precipitate was washed with light petroleum (3 x 10 mL) and dried under vacuum to afford the phosphonium salt **88** as a white solid (6.12 g, 93%); m.p. 180–182 °C (lit. m.p. 179–181 °C).³⁰⁵ The spectroscopic data matched that provided by Graden.³⁰⁵

¹H NMR (400 MHz, DMSO): δ 7.93 (3 H, m), 7.79 (12 H, m), 6.65 (1 H, m), 6.12 (1 H, d, J = 15.4 Hz), 4.87 (1 H, d, J = 7.8 Hz), 4.83 (1 H, d, J = 7.8 Hz), 3.63 (3 H, s) ppm.

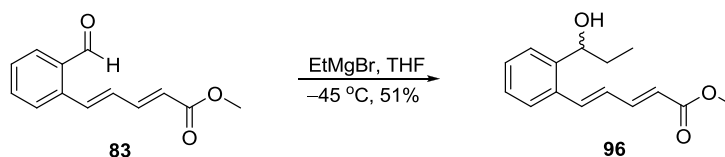
9.2.5 Wittig reaction with the lactol **87** and the phosphonium salt **88**



n-BuLi (1.6 M in hexanes, 0.91 mL, 1.45 mmol, 1.0 eq.) was added dropwise to the phosphonium salt **88** (640 mg, 1.45 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 minutes, then allowed to warm to room temperature and stirred for a further 10 minutes. A solution of the lactol **87** (197 mg, 1.45 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (2 mL) was added dropwise over 10 minutes and the mixture was stirred at room temperature for 16 hours. The mixture was concentrated under reduced pressure to afford an orange solid. The solid was subjected to column chromatography. Elution with 50% ethyl acetate/light petroleum gave the *benzodiene* as a colourless oil (123 mg, 39%). The oil was dissolved in anhydrous dichloromethane (10 mL) and reacted with activated manganese dioxide (492 mg, 5.66 mmol, 10.0 eq.) at room temperature for 24 hours. The resulting mixture was filtered and the filtrate concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 20% ethyl acetate/light petroleum afforded the aldehyde **83** as a yellow oil (93 mg, 76%).

¹H NMR (400 MHz, CDCl₃): δ 10.21 (1 H, s), 7.85 (1 H, d, *J* = 15.5 Hz), 7.80 (1 H, d, *J* = 7.6 Hz), 7.64 (1 H, d, *J* = 7.6 Hz), 7.56 (1 H, m), 7.49 (1 H, dd, *J* = 11.1, 15.4 Hz), 7.46 (1 H, m), 6.81 (1 H, dd, *J* = 11.1, 15.5 Hz), 6.02 (1 H, d, *J* = 15.4 Hz), 3.77 (3 H, s) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 192.5 (CH), 167.2 (C), 144.4 (CH), 138.0 (C), 136.5 (CH), 133.8 (CH), 133.2 (CH), 133.2 (C), 130.8 (CH), 128.9 (CH), 127.3 (CH), 122.6 (CH), 51.7 (CH₃) ppm; **ATR-FTIR**: 1694 (aldehyde and ester: C=O) cm⁻¹; **HRMS (ASAP)**: [*M*⁺] C₁₃H₁₂O₃ requires 217.0865; found: 217.0857.

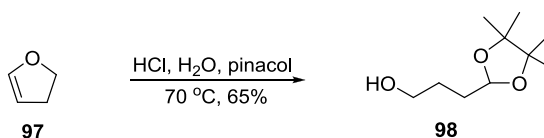
9.2.6 Addition of ethylmagnesium bromide to the aldehyde **83**



Ethylmagnesium bromide (1 M, 0.42 mL, 0.42 mmol, 1.0 eq.) was added dropwise to a solution of the aldehyde **83** (90 mg, 0.42 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (3 mL) at $-45\text{ }^{\circ}\text{C}$. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. The reaction was quenched with a saturated aqueous solution of NH_4Cl (4 mL) and the mixture stirred for 30 minutes. The reaction mixture was diluted with ether (30 mL), washed with deionised water (2 x 20 mL), dried and concentrated under reduced pressure to give a light brown liquid. The liquid was subjected to column chromatography. Elution with 30% ethyl acetate/light petroleum afforded the alcohol **96** as a colourless oil (52 mg, 51%).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.51 (3 H, m), 7.29 (3 H, m), 6.78 (1 H, dd, $J = 11.1, 15.3$ Hz), 5.99 (1 H, d, $J = 15.3$ Hz), 4.94 (1 H, t, $J = 6.3$ Hz), 3.77 (3 H, s), 1.98 (1 H, br. s), 1.77 (2 H, m), 0.95 (3 H, t, $J = 7.4$ Hz) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 167.6 (C), 145.1 (CH), 142.7 (C), 137.6 (CH), 133.9 (C), 129.2 (CH), 128.3 (CH), 127.7 (CH), 126.3 (CH), 126.3 (CH), 121.2 (CH), 72.6 (CH), 51.8 (CH_3), 31.7 (CH_2), 10.4 (CH_3) ppm; **ATR-FTIR**: 3443 (OH) and 1709 ($\text{C}=\text{O}$) cm^{-1} ; **HRMS** (**ASAP**): $[\text{M}^+]$ $\text{C}_{15}\text{H}_{18}\text{O}_3$ requires 247.1334; found: 247.1333.

9.2.7 Acid-catalysed reaction of pinacol and 2,3-dihydrofuran

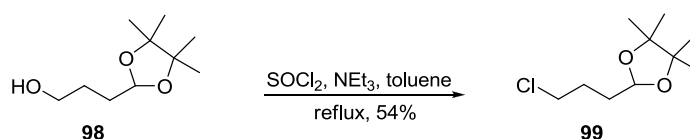


Adapting the procedure from Stowell and Polito,²⁰¹ a solution of 2,3-dihydrofuran (10.05 g, 0.14 mol, 1.0 eq.), HCl (32% w/v, 3.26 mL) and deionised water (32 mL) was stirred at room temperature for 1 hour. Pinacol (20.33 g, 0.17 mol, 1.2 eq.) was dissolved in warm deionised water (72 mL), added dropwise and the solution was heated at $70\text{ }^{\circ}\text{C}$ for 15 hours. Phenolphthalein indicator (0.5 mL) was added and the reaction mixture was neutralised with 4 M NaOH (15 mL). The mixture was extracted

with ether (100 mL), dried and concentrated under reduced pressure to afford a pink oil. The oil was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 50% ethyl acetate/light petroleum afforded compound **98** as a yellow oil (17.55 g, 65%). The spectroscopic data matched that provided by Stowell and Polito.²⁰¹

¹H NMR (400 MHz, CDCl₃): δ 4.97 (1 H, t, *J* = 4.4 Hz), 3.54 (2 H, t, *J* = 5.4 Hz), 2.96 (1 H, br. s), 1.59 (4 H, m), 1.10 (12 H, s) ppm.

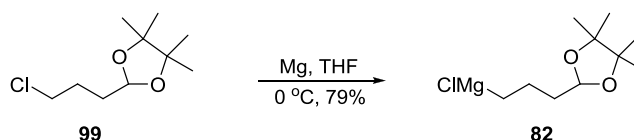
9.2.8 Treatment of the alcohol **98** with thionyl chloride



Thionyl chloride (2.53 g, 1.54 mL, 0.02 mol, 1.0 eq.) was added dropwise to the alcohol **98** (4.00 g, 0.02 mol, 1.0 eq.) and triethylamine (2.15 g, 0.02 mol, 1.1 eq.) in toluene (55 mL) at 0 °C. The solution was then heated under reflux and stirred for 1 hour. The reaction mixture was diluted with ether (60 mL), washed with deionised water (3 x 30 mL), dried and concentrated under reduced pressure to afford a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 10% ethyl acetate/light petroleum afforded compound **99** as a yellow oil (2.37 g, 54%).

¹H NMR (400 MHz, CDCl₃): δ 5.06 (1 H, t, *J* = 5.0 Hz), 3.58 (2 H, t, *J* = 6.7 Hz), 1.88 (2 H, m), 1.74 (2 H, m), 1.19 (12 H, s) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 100.3 (CH), 81.8 (C), 45.1 (CH₂), 33.7 (CH₂), 27.8 (CH₂), 24.4 (CH₃), 22.2 (CH₃) ppm; **HRMS (ASAP)**: [M⁺] C₁₀H₁₉ClO₂ requires 207.0941; found: 207.0941.

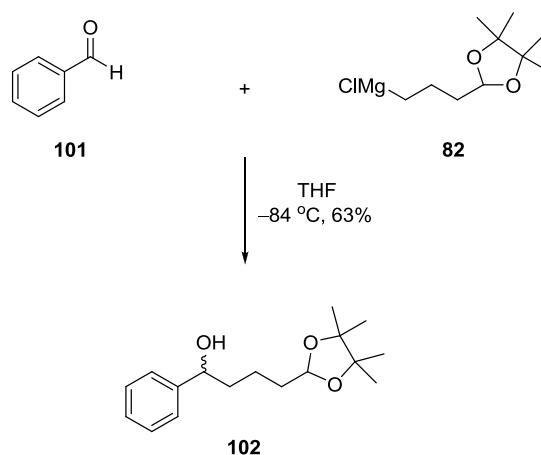
9.2.9 Preparation of the Grignard reagent **82**



A solution of compound **99** (1.16 g, 5.61 mmol, 1.0 eq.) and magnesium turnings (0.38 g, 15.71 mmol, 2.8 eq.) in anhydrous tetrahydrofuran (1 mL) was stirred at room temperature with gradual addition of 1,2-dibromoethane (0.21 g, 1.12 mmol,

0.2 eq.) over 5 minutes. The solution was cooled to 0 °C upon initiation, diluted with anhydrous tetrahydrofuran (5 mL) and stirred at this temperature for 19 hours. After this time, the Grignard reagent **82** was afforded in 79% yield. The concentration of the Grignard was 0.79 M, as determined by titration with BHT and 1,10-phenanthroline.

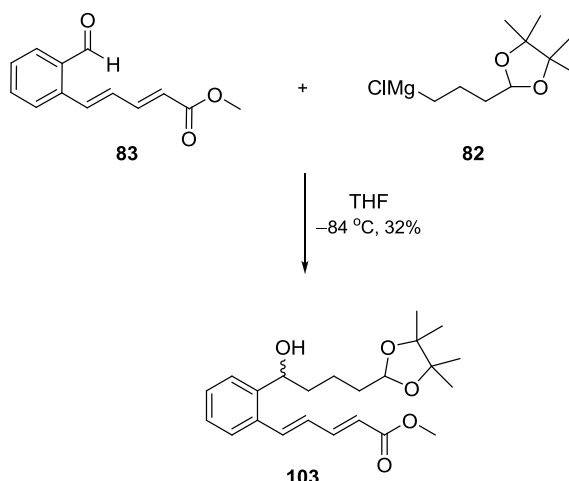
9.2.10 Addition of the Grignard reagent **82** to benzaldehyde



The Grignard reagent **82** (0.79 M, 1.19 mL, 0.94 mmol, 1.0 eq.) was added dropwise to benzaldehyde (100 mg, 0.94 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (2 mL) at $-84\text{ }^\circ\text{C}$ and the mixture was stirred for 6 hours. The reaction was quenched with a saturated aqueous solution of NH_4Cl (4 mL) and stirred for 30 minutes. The reaction mixture was diluted with dichloromethane (50 mL), washed with deionised water (2 x 20 mL), dried and concentrated under reduced pressure to afford a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 40% ethyl acetate/light petroleum afforded compound **102** as a colourless oil (165 mg, 63%).

^1H NMR (400 MHz, CDCl_3): δ 7.23 (4 H, m), 7.22 (1 H, m), 4.96 (1 H, t, $J = 5.0$ Hz), 4.60 (1 H, dd, $J = 5.6, 7.6$ Hz), 1.96 (1 H, br. s), 1.70 (2 H, m), 1.56 (2 H, m), 1.49 (1 H, m), 1.34 (1 H, m), 1.12 (12 H, s) ppm; **^{13}C NMR** (100 MHz, CDCl_3): δ 145.0 (C), 128.5 (CH), 127.6 (CH), 126.0 (CH), 100.9 (CH), 81.8 (C), 81.8 (C), 74.5 (CH), 39.1 (CH_2), 36.2 (CH_2), 24.4 (CH_3), 22.2 (CH_3), 21.0 (CH_2) ppm; **ATR-FTIR**: 3446 (OH) cm^{-1} ; **HRMS (ASAP)**: $[\text{M}^+]$ $\text{C}_{17}\text{H}_{26}\text{O}_3$ requires 278.1882; found: 278.1869.

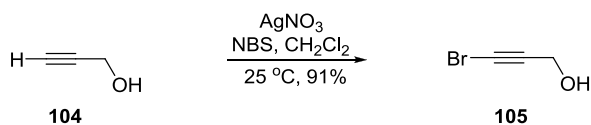
9.2.11 Addition of the Grignard reagent **82** to compound **83**



The Grignard reagent **82** (0.79 M, 1.00 mL, 0.79 mmol, 1.0 eq.) was added dropwise to the aldehyde **83** (170 mg, 0.79 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (2 mL) at -84 °C and the mixture was stirred for 5 hours. The reaction was quenched with a saturated aqueous solution of NH₄Cl (4 mL) and stirred for 30 minutes. The reaction mixture was diluted with dichloromethane (30 mL), washed with deionised water (2 x 20 mL), dried and concentrated under reduced pressure to afford a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 30% ethyl acetate/light petroleum afforded the alcohol **103** as a yellow oil (98 mg, 32%).

¹H NMR (400 MHz, CDCl₃): δ 7.42 (3 H, m), 7.22 (3 H, m), 6.72 (1 H, dd, *J* = 11.1, 15.3 Hz), 5.92 (1 H, d, *J* = 15.3 Hz), 4.95 (2 H, m), 3.70 (3 H, s), 2.13 (1 H, br. s), 1.69 (4 H, m), 1.54 (2 H, m), 1.10 (12 H, s) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 167.6 (C), 145.1 (CH), 142.9 (C), 137.5 (CH), 133.7 (C), 129.2 (CH), 128.3 (CH), 127.6 (CH), 126.3 (CH), 121.2 (CH), 100.8 (CH), 81.9 (C), 81.8 (C), 71.1 (CH), 51.7 (CH₃), 38.6 (CH₂), 36.0 (CH₂), 24.4 (CH₃), 22.2 (CH₃), 21.0 (CH₂) ppm; **ATR-FTIR**: 3455 (OH) and 1715 (C=O) cm⁻¹; **HRMS (ASAP)**: [M⁺] C₂₃H₃₂O₅ requires 388.2250; found: 388.2234.

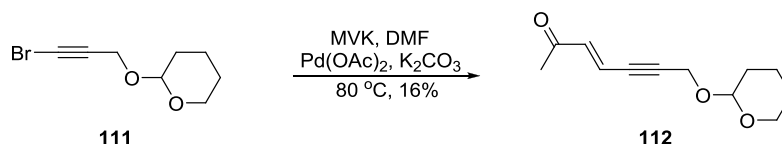
9.2.12 Synthesis of 3-bromopropargyl alcohol



Adapting the procedure by Gjorstrup,²⁰⁴ propargyl alcohol (3.26 g, 0.06 mol, 1.0 eq.) was added dropwise to a solution of *N*-bromosuccinimide (11.18 g, 0.06 mol, 1.08 eq.) and silver nitrate (0.99 g, 5.81 mmol, 0.1 eq.) in acetone (100 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. The mixture was diluted with ether (3 x 40 mL), washed with deionised water (2 x 50 mL), dried and concentrated under reduced pressure to afford a colourless oil. The oil was subjected to column chromatography. Elution with 30% ethyl acetate/light petroleum gave 3-bromopropargyl alcohol **105** as a colourless oil (7.14 g, 91%). The ¹H NMR spectrum matched that provided by Gjorstrup.²⁰⁴

¹H NMR (400 MHz, CDCl₃): δ 4.24 (2 H, s), 2.80 (1 H, br. s) ppm.

9.2.13 Heck reaction with methyl vinyl ketone and compound 111

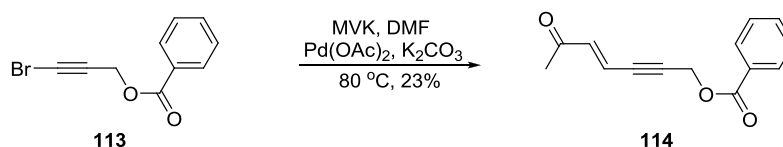


A mixture of the bromide **111** (610 mg, 2.78 mmol, 1.0 eq.), methyl vinyl ketone (1.95 g, 27.84 mmol, 10.0 eq.), potassium carbonate (962 mg, 6.96 mmol, 2.5 eq.), Pd(OAc)₂ (31 mg, 0.14 mmol, 5 mol%) and BHT (1 crystal) was heated at 80 °C in anhydrous dimethylformamide (5 mL) for 2 hours. The resulting mixture was filtered. The filtrate was diluted with ether (50 mL), washed with aqueous CuSO₄ (2 x 30 mL), washed with deionised water (30 mL) and dried. The ethereal layer was concentrated under reduced pressure to give a dark, brown liquid. The liquid was subjected to column chromatography. The column was conditioned with triethylamine (1%). Elution with 30% ethyl acetate/light petroleum afforded the ketone **112** as a yellow oil (93 mg, 16%).

¹H NMR (400 MHz, CDCl₃): δ 6.59 (1 H, t, *J* = 1.9, 16.2 Hz), 6.46 (1 H, d, *J* = 16.2 Hz), 4.78 (1 H, t, *J* = 3.4 Hz), 4.44 (1 H, dd, *J* = 1.9, 16.4 Hz), 4.37 (1 H, dd,

$J = 1.9, 16.4$ Hz), 3.82 (1 H, m), 3.54 (1 H, m), 2.24 (3 H, s), 1.82 (3 H, m), 1.61 (2 H, m), 1.54 (1 H, m) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 197.0 (C), 138.5 (CH), 123.3 (CH), 97.2 (CH), 96.0 (C), 83.1 (C), 62.1 (CH_2), 54.7 (CH_2), 30.3 (CH_2), 27.7 (CH_3), 25.4 (CH_2), 19.0 (CH_2) ppm; **ATR-FTIR**: 1678 ($\text{C}=\text{O}$) cm^{-1} ; **HRMS (ASAP)**: Molecular ion not found.

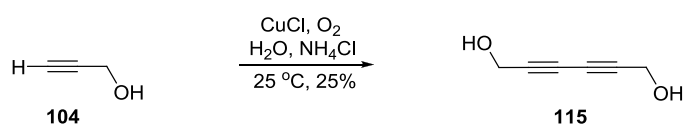
9.2.14 Heck reaction with methyl vinyl ketone and compound **113**



A mixture of the bromide **113** (330 mg, 1.38 mmol, 1.0 eq.), methyl vinyl ketone (968 mg, 13.80 mmol, 10.0 eq.), potassium carbonate (477 mg, 3.45 mmol, 2.5 eq.), $\text{Pd}(\text{OAc})_2$ (16 mg, 0.07 mmol, 5 mol%) and BHT (1 crystal) was heated at 80 °C in anhydrous dimethylformamide (5 mL) for 2 hours. The resulting mixture was filtered. The filtrate was diluted with ether (25 mL), washed with aqueous CuSO_4 (2 x 15 mL), washed with deionised water (15 mL) and dried. The ethereal layer was concentrated under reduced pressure to give a dark, brown liquid. The liquid was subjected to column chromatography. Elution with 30% ethyl acetate/light petroleum afforded the ketone **114** as a yellow oil (72 mg, 23%).

^1H NMR (400 MHz, CDCl_3): δ 8.06 (2 H, d, $J = 7.8$ Hz), 7.59 (1 H, t, $J = 7.9$ Hz), 7.46 (2 H, dd, $J = 7.8, 7.9$ Hz), 6.63 (1 H, dd, $J = 1.9, 16.2$ Hz), 6.52 (1 H, d, $J = 16.2$ Hz), 5.09 (2 H, d, $J = 1.9$ Hz), 2.26 (3 H, s) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 196.9 (C), 165.9 (C), 139.1 (CH), 133.6 (CH), 130.0 (CH), 129.4 (C), 128.6 (CH), 122.7 (CH), 93.3 (C), 83.7 (C), 53.1 (CH_2), 27.9 (CH_3) ppm; **ATR-FTIR**: 1724 (ester $\text{C}=\text{O}$), 1677 (ketone $\text{C}=\text{O}$) cm^{-1} ; **HRMS (ASAP)**: Molecular ion not found.

9.2.15 Glaser coupling of propargyl alcohol

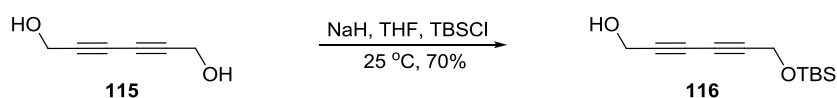


Following the procedure by Brandsma,²⁰⁵ a mixture of propargyl alcohol (28.00 g, 0.50 mol, 1.0 eq.), CuCl (4.94 g, 0.05 mol, 0.1 eq.) and NH_4Cl (21.37 g, 0.40 mol,

0.8 eq.) in water (65 mL) was stirred at room temperature for 22 hours under a constant supply of air. HCl (32% w/v, 6 mL) was then added dropwise to dissolve the Cu(OH)Cl solution and the mixture was stirred at room temperature for an additional 10 minutes. The reaction mixture was diluted with dichloromethane (4 x 80 mL) and washed with deionised water (2 x 10 mL). The organic layer was dried and the solvent removed under reduced pressure to afford a brown solid. The solid was recrystallised from chloroform/ethyl acetate to give the diol **115** as white needles (13.75 g, 25%); m.p. 107–108 °C (lit m.p. 108–109 °C).²⁰⁵ The ¹H NMR spectrum matched the spectroscopic data provided by Brandsma.²⁰⁵

¹H NMR (400 MHz, DMSO): δ 5.39 (2 H, t, *J* = 2.4 Hz), 4.18 (4 H, d, *J* = 2.4 Hz) ppm.

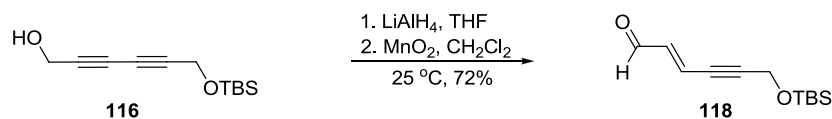
9.2.16 Monosilylation of 2,4-hexadiyne-1,6-diol



Following the procedure by Trost and Livingston,²⁰⁸ 60% NaH in mineral oil (1.16 g, 27.25 mmol, 1.0 eq.) was added in small portions to the diol **115** (3.00 g, 27.25 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (60 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours upon which TBSCl (4.11 g, 27.25 mmol, 1.0 eq.) was added in small portions. The mixture was stirred for a further 3 hours, then quenched with methanol (6 mL). The reaction mixture was diluted with ether (4 x 50 mL), washed with deionised water (2 x 50 mL), dried and concentrated under reduced pressure to afford a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 40% ethyl acetate/light petroleum gave compound **116** as a yellow liquid (4.28 g, 70%). The spectroscopic data matched that reported by Trost and Livingston.²⁰⁸

¹H NMR (400 MHz, CDCl₃): δ 4.38 (2 H, s), 4.34 (2 H, s), 1.78 (1 H, br. s), 0.90 (9 H, s), 0.12 (6 H, s) ppm.

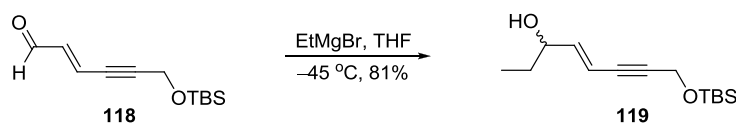
9.2.17 Preparation of the aldehyde **118**



Adapting the procedure by Trost and Livingston,²⁰⁸ LiAlH₄ (213 mg, 5.62 mmol, 1.0 eq.) was added in small portions to the alcohol **116** (1.26 g, 5.62 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (12 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction was quenched with a saturated aqueous solution of sodium sulfate (3 mL) and ethyl acetate (4 mL) and the resulting precipitate was removed by filtration. The filtrate was diluted with ether (3 x 40 mL), washed with deionised water (40 mL), dried and concentrated under reduced pressure to afford the alcohol **117** as a yellow oil (1.03 g, 85%). The crude oil was then taken up in anhydrous dichloromethane (30 mL) and stirred at room temperature with activated manganese dioxide (3.95 g, 45.49 mmol, 10.0 eq.) for three and a half days. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the aldehyde **118** as a yellow oil (0.87 g, 85%). The ¹H NMR spectrum matched the spectrum of the aldehyde **118** provided by Trost and Livingston.²⁰⁸

¹H NMR (400 MHz, CDCl₃): δ 9.53 (1 H, d, *J* = 7.7 Hz), 6.72 (1 H, d, *J* = 15.9 Hz), 6.43 (1 H, dd, *J* = 7.7, 15.9 Hz), 4.50 (2 H, s), 0.89 (9 H, s), 0.11 (6 H, s) ppm.

9.2.18 Addition of ethylmagnesium bromide to the aldehyde **118**

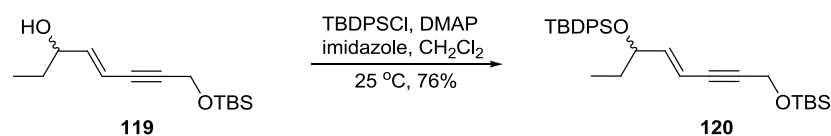


Ethylmagnesium bromide (0.82 M, 2.63 mL, 2.15 mmol, 2.3 eq.) was added dropwise to the aldehyde **118** (210 mg, 0.94 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (5 mL) at -45 °C and the mixture was stirred for 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred for a further four and a half hours. A saturated aqueous solution of NH₄Cl (3 mL) was then added dropwise at 0 °C and the mixture was stirred for 30 minutes. The reaction mixture was diluted with ether (40 mL), washed with deionised water (3 x 30 mL), dried and

concentrated under reduced pressure to afford an orange liquid. The liquid was subjected to radial chromatography and the column was conditioned with triethylamine (1%). Elution with light petroleum gave the alcohol **119** as a yellow liquid (193 mg, 81%).

¹H NMR (400 MHz, CDCl₃): δ 6.10 (1 H, dd, *J* = 6.1, 15.9 Hz), 5.71 (1 H, d, *J* = 15.9 Hz), 4.40 (2 H, s), 4.07 (1 H, m), 1.83 (1 H, br. s), 1.55 (2 H, m), 0.94 (3 H, t, *J* = 7.4 Hz), 0.90 (9 H, s), 0.12 (6 H, s) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 145.6 (CH), 109.8 (CH), 88.6 (C), 82.9 (C), 73.7 (CH), 52.3 (CH₂), 30.0 (CH₂), 26.0 (CH₃), 18.5 (C), 9.6 (CH₃), -5.0 (CH₃) ppm; **ATR-FTIR**: 3398 (OH) cm⁻¹; **Elemental Analysis**: Found: C, 66.09%; H, 10.35%. C₁₄H₂₆O₄Si calculated C, 66.09%; H, 10.30%).

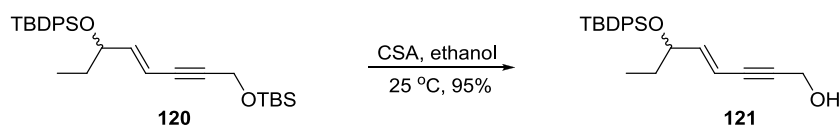
9.2.19 Silylation of the alcohol **119**



A mixture of the alcohol **119** (770 mg, 3.03 mmol, 1.0 eq.), imidazole (412 mg, 6.05 mmol, 2.0 eq.), TBDPSCI (998 mg, 3.63 mmol, 1.2 eq.) and DMAP (37 mg, 0.30 mmol, 0.1 eq.) was stirred in anhydrous dichloromethane (30 mL) at room temperature for 21 hours. The reaction mixture was diluted with ether (50 mL), washed with deionised water (30 mL), dried and concentrated under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with light petroleum afforded compound **120** as a colourless oil (1.13 g, 76%).

¹H NMR (400 MHz, CDCl₃): δ 7.63 (4 H, m), 7.38 (6 H, m), 6.05 (1 H, dd, *J* = 6.0, 15.9 Hz), 5.55 (1 H, d, *J* = 15.9 Hz), 4.52 (2 H, s), 4.16 (1 H, m), 1.46 (2 H, m), 1.07 (9 H, s), 0.92 (9 H, s), 0.76 (3 H, t, *J* = 7.4 Hz), 0.13 (6 H, s) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 145.6 (CH), 136.0 (CH), 134.7 (C), 134.0 (C), 129.8 (CH), 127.7 (CH), 109.3 (CH), 88.1 (C), 83.4 (C), 74.5 (CH), 52.7 (CH₂), 30.5 (CH₂), 27.2 (CH₃), 26.0 (CH₃), 19.5 (C), 18.5 (C), 8.7 (CH₃), -4.9 (CH₃) ppm; **HRMS (ASAP)**: [M⁺] C₃₀H₄₄O₂Si₂ requires 493.2958; found: 493.2971.

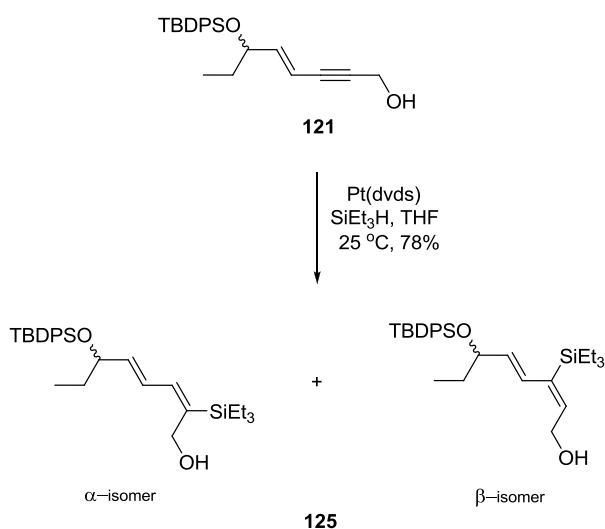
9.2.20 Synthesis of the alcohol **121**



A mixture of compound **120** (850 mg, 1.72 mmol, 1.0 eq.) and CSA (5 mg, 0.02 mmol) in ethanol (20 mL) was stirred at room temperature for 12 hours. The reaction mixture was diluted with ether (40 mL), washed with deionised water (2 x 30 mL), dried and concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 30% ethyl acetate/light petroleum afforded the alcohol **121** as a colourless oil (620 mg, 95%).

¹H NMR (400 MHz, CDCl₃): δ 7.65 (4 H, m), 7.39 (6 H, m), 6.10 (1 H, dd, *J* = 5.8, 15.9 Hz), 5.59 (1 H, d, *J* = 15.9 Hz), 4.37 (2 H, s), 4.19 (1 H, m), 1.69 (1 H, br. s), 1.46 (2 H, m), 1.08 (9 H, s), 0.77 (3 H, t, *J* = 7.4 Hz) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 146.2 (CH), 136.0 (CH), 134.3 (C), 133.9 (C), 129.8 (CH), 127.7 (CH), 108.9 (CH), 87.4 (C), 84.3 (C), 74.4 (CH), 51.8 (CH₂), 30.14 (CH₂), 27.2 (CH₃), 19.5 (C), 8.6 (CH₃) ppm; **ATR-FTIR**: 3402 (OH) cm⁻¹; **HRMS (ESI)**: [M+23 (Na)]⁺ C₃₆H₆₀O₂Si₃ requires 401.1913; found: 401.1926.

9.2.21 Hydrosilylation of compound **121**

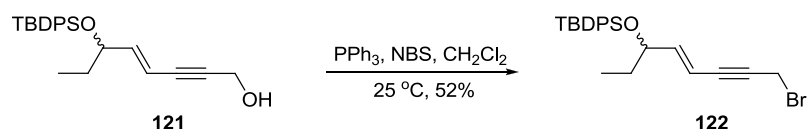


A mixture of the alcohol **121** (81 mg, 0.21 mmol, 1.0 eq.), triethylsilane (27 mg, 0.24 mmol, 1.1 eq.) and Pt(dvds) (5 mg, 0.01 mmol, 6 mol%) in anhydrous

tetrahydrofuran (1 mL) was stirred at room temperature for 15 hours. The reaction mixture was diluted with ether (5 mL), washed with deionised water (5 mL), dried and concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with light petroleum afforded a colourless oil that was a 65:35 mixture of the α and β -isomers of **125** respectively (83 mg, 78%).

^1H NMR (400 MHz, CDCl_3): **Key signals** δ 6.26 (1 H, dd, $J = 11.0, 14.6$ Hz α -isomer), 6.21 (1 H, d, $J = 11.0$ Hz α -isomer), 6.03 (1 H, d, $J = 15.9$ Hz β -isomer), 5.81 (1 H, t, $J = 5.8$ Hz β -isomer), 5.68 (1 H, dd, $J = 6.8, 14.6$ Hz α -isomer), 5.50 (1 H, dd, $J = 6.8, 15.9$ Hz β -isomer) ppm; **ATR-FTIR**: 3401 (OH) cm^{-1} ; **HRMS (ESI)**: $[\text{M}+23 (\text{Na})]^+$ $\text{C}_{30}\text{H}_{46}\text{O}_2\text{Si}_2$ requires 517.2934; found: 517.2941.

9.2.22 Synthesis of compound **122** via an Appel reaction

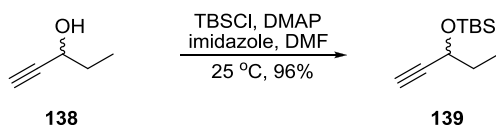


Triphenylphosphine (386 mg, 1.47 mmol, 0.9 eq.) and *N*-bromosuccinimide (321 mg, 1.80 mmol, 1.1 eq.) were added to the alcohol **121** (620 mg, 1.64 mmol, 1.0 eq.) in anhydrous dichloromethane (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 8 hours. The mixture was diluted with dichloromethane (20 mL) and washed with deionised water (3 x 20 mL). The organic layer was dried and concentrated under reduced pressure to afford a yellow solid. The solid was subjected to radial chromatography and the column was conditioned with triethylamine (1%). Elution with light petroleum afforded compound **122** as colourless oil (376 mg, 52%).

^1H NMR (400 MHz, CDCl_3): δ 7.66 (4 H, m), 7.39 (6 H, m), 6.11 (1 H, dd, $J = 5.6, 15.9$ Hz), 5.58 (1 H, d, $J = 15.9$ Hz), 4.20 (1 H, m), 4.06 (2 H, s), 1.44 (2 H, m), 1.07 (9 H, s), 0.76 (3 H, t, $J = 7.4$ Hz) ppm; **^{13}C NMR** (100 MHz, CDCl_3): δ 147.3 (CH), 136.0 (CH), 134.3 (C), 133.9 (C), 129.8 (CH), 127.7 (CH), 108.6 (CH), 85.4 (C), 84.3 (C), 74.3 (CH), 30.1 (CH_2), 27.2 (CH_3), 19.5 (C), 15.7 (CH_2), 8.6 (CH_3) ppm; **HRMS (ASAP)**: $[\text{M}^+]$ $\text{C}_{24}\text{H}_{29}\text{OBrSi}$ requires 441.1249; found: 441.1254.

9.3 Chapter 3 experimental procedures

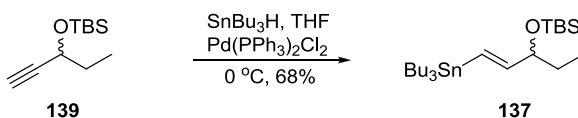
9.3.1 Silylation of 1-pentyn-3-ol



A mixture of 1-pentyn-3-ol (500 mg, 5.94 mmol, 1.0 eq.), imidazole (607 mg, 8.92 mmol, 1.5 eq.) and DMAP (73 mg, 0.59 mmol, 0.1 eq.) in anhydrous dimethylformamide (7 mL) was stirred at 0 °C for 10 minutes. TBSCl (940 mg, 6.12 mmol, 1.0 eq.) was added in portions and the mixture was allowed to warm to room temperature and stirred for 23 hours. The reaction mixture was diluted with ether (10 mL), washed with an aqueous CuSO₄ solution (2 mL) and washed with deionised water (2 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with light petroleum afforded compound **139** as a colourless oil (1.13 g, 96%). The spectroscopic data matched that reported in the literature.²¹¹

¹H NMR (400 MHz, CDCl₃): δ 4.27 (1 H, t, *J* = 6.3 Hz), 2.35 (1 H, s), 1.68 (2 H, m), 0.96 (3 H, t, *J* = 7.4 Hz), 0.89 (9 H, s), 0.12 (3 H, s), 0.10 (3 H, s) ppm.

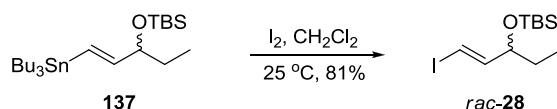
9.3.2 Hydrostannation of the alkyne **139**



Following a similar procedure to Zhang et al.,³⁰⁶ Pd(PPh₃)₂Cl₂ (42 mg, 0.06 mmol, 2 mol%) was added in one portion to the alkyne **139** (600 mg, 3.02 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (9 mL) at 0 °C. The reaction mixture was stirred for 5 minutes at 0 °C, treated with tributyltin hydride (968 mg, 3.33 mmol, 1.1 eq.) and stirred for a further 10 minutes. The reaction mixture was concentrated under reduced pressure to afford a brown oil. The oil was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with light petroleum afforded the stannane **137** as a colourless oil (1.01 g, 68%). The spectroscopic data matched that reported in the literature.²¹¹

¹H NMR (400 MHz, CDCl₃): δ 6.03 (1 H, d, *J* = 19.1 Hz), 5.90 (1 H, dd, *J* = 5.7, 19.1 Hz), 3.96 (1 H, m), 1.47–1.52 (10 H, m), 1.25–1.36 (7 H, m), 0.86–0.94 (24 H, m), 0.05 (3 H, s), 0.04 (3 H, s) ppm.

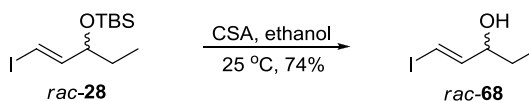
9.3.3 Treatment of compound 137 with iodine



Iodine (214 mg, 1.69 mmol, 1.1 eq.) was added in one portion to compound **137** (750 mg, 1.53 mmol, 1.0 eq.) in anhydrous ether (10 mL) at 0 °C. The mixture was allowed to warm to room temperature over 22 hours. The reaction mixture was washed with a solution of sodium metabisulfite (5% aq., 2 mL) and deionised water (2 x 10 mL) and then dried. The solvent was removed under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with light petroleum afforded *rac*-**28** as a colourless oil (405 mg, 81%). The spectroscopic data matched that reported in the literature.²¹¹

¹H NMR (400 MHz, CDCl₃): δ 6.51 (1 H, dd, *J* = 5.9, 14.4 Hz), 6.19 (1 H, d, *J* = 14.4 Hz), 4.02 (1 H, m), 1.50 (2 H, m), 0.90 (9 H, s), 0.89 (3 H, t, *J* = 7.4 Hz), 0.05 (3 H, s), 0.04 (3 H, s) ppm.

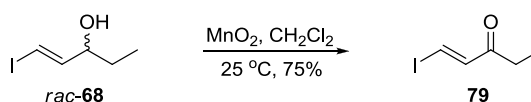
9.3.4 Deprotection of *rac*-28



A mixture of *rac*-**28** (160 mg, 0.49 mmol, 1.0 eq.) and CSA (1 mg, 5.70 μ mol) in ethanol (3 mL) was stirred at room temperature for 24 hours. The reaction mixture was washed with a solution of sodium bicarbonate (5% aq., 5 mL) and deionised water (2 x 10 mL) and then dried. The solvent was removed under reduced pressure to give *rac*-**68** as a colourless liquid (77 mg, 74%). The ¹H NMR spectrum matched the spectroscopic data provided by Amin and co-workers.¹⁸⁵

^1H NMR (400 MHz, CDCl_3): δ 6.56 (1 H, dd, $J = 6.3, 14.5$ Hz), 6.33 (1 H, d, $J = 14.5$ Hz), 4.01 (1 H, m), 2.17 (1 H, br. s), 1.54 (2 H, m), 0.92 (3 H, t, $J = 7.4$ Hz) ppm.

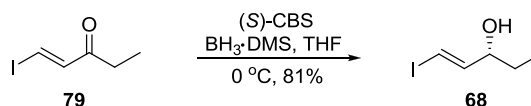
9.3.5 Oxidation of *rac*-68



Activated manganese dioxide (3.12 g, 35.84 mmol, 10.0 eq.) was added in one portion to *rac*-68 (760 mg, 3.58 mmol, 1.0 eq.) in anhydrous dichloromethane (15 mL). The reaction mixture was stirred at room temperature for 32 hours. The mixture was filtered and the filtrate concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography. Elution with 30% ethyl acetate/light petroleum afforded the ketone **79** as a yellow oil (565 mg, 75%). The spectroscopic data matched that reported in the literature.¹⁸⁵

^1H NMR (400 MHz, CDCl_3): δ 7.81 (1 H, d, $J = 15.0$ Hz), 7.17 (1 H, d, $J = 15.0$ Hz), 2.54 (2 H, q, $J = 7.3$ Hz), 1.10 (3 H, t, $J = 7.3$ Hz) ppm.

9.3.6 Asymmetric reduction of the ketone **79**

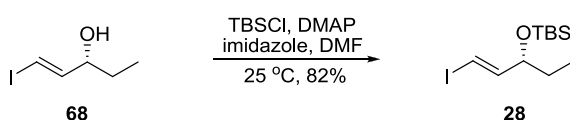


(*S*)-(-)-2-Methyl-CBS-oxazaborolidine (16 mg, 0.06 mmol, 10 mol%) was added to a solution of $\text{BH}_3\cdot\text{DMS}$ (26 mg, 32.52 μL , 0.34 mmol, 0.6 eq.) in anhydrous tetrahydrofuran (1 mL) at room temperature and stirred for 15 minutes. The solution was cooled to 0 $^\circ\text{C}$ and the ketone **79** (120 mg, 0.57 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (2 mL) was added dropwise over 2 hours. The reaction mixture was stirred at 0 $^\circ\text{C}$ for a further hour. Methanol (2 mL) and a saturated aqueous solution of NH_4Cl (2 mL) were then added successively. The mixture was diluted with dichloromethane (15 mL). The organic layer was dried and concentrated under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography. Elution with 20% ethyl acetate/light petroleum afforded the

alcohol **68** as a colourless oil (98 mg, 81%) in 96% *ee*. The ^1H NMR spectrum matched the spectroscopic data provided by Amin and co-workers.¹⁸⁵

^1H NMR (400 MHz, CDCl_3): δ 6.56 (1 H, dd, $J = 6.3, 14.5$ Hz), 6.33 (1 H, d, $J = 14.5$ Hz), 4.01 (1 H, m), 2.17 (1 H, br. s), 1.54 (2 H, m), 0.92 (3 H, t, $J = 7.4$ Hz) ppm; $[\alpha]_D^{25} = -0.44$ ($c = 1.00$, CH_3OH), lit. $[\alpha]_D^{25} = -0.46$ ($c = 1.50$, CH_3OH).²¹²

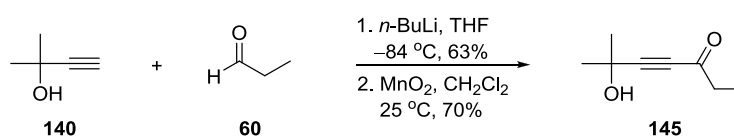
9.3.7 Silylation of the alcohol **68**



A mixture of the alcohol **68** (98 mg, 0.46 mmol, 1.0 eq.), imidazole (47 mg, 0.69 mmol, 1.5 eq.) and DMAP (6 mg, 0.05 mmol, 0.1 eq.) in anhydrous dimethylformamide (4 mL) was stirred at 0 °C for 10 minutes. TBSCl (70 mg, 0.46 mmol, 1.0 eq.) was added in small portions and the mixture was allowed to warm to room temperature and stirred for 24 hours. The reaction mixture was diluted with ether (10 mL), washed with an aqueous CuSO_4 solution (2 mL) and washed with deionised water (2 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with light petroleum afforded compound **28** as a colourless oil (124 mg, 82%). The spectroscopic data matched that reported by Rodriquez and Spur.²¹¹

^1H NMR (400 MHz, CDCl_3): δ 6.51 (1 H, dd, $J = 5.9, 14.4$ Hz), 6.19 (1 H, d, $J = 14.4$ Hz), 4.02 (1 H, m), 1.50 (2 H, m), 0.90 (9 H, s), 0.89 (3 H, t, $J = 7.4$ Hz), 0.05 (3 H, s), 0.04 (3 H, s) ppm.

9.3.8 Addition of 2-methyl-3-butyn-2-ol to propionaldehyde

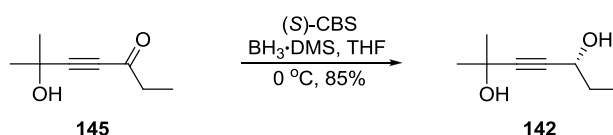


Following a similar procedure to Muehlebach et al.,³⁰⁷ *n*-BuLi (1.6 M in hexanes, 15.75 mL, 25.20 mmol, 2.0 eq.) was added dropwise to 2-methyl-3-butyn-2-ol

(1.06 g, 12.60 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (30 mL) at -84°C . The solution was stirred for 1 hour at this temperature followed by dropwise addition of propionaldehyde (732 mg, 12.60 mmol, 1.0 eq.). The reaction mixture was allowed to warm to room temperature over two and a half hours. A saturated aqueous solution of NH_4Cl (10 mL) was then added in one portion. The mixture was diluted with ethyl acetate (50 mL) and washed with deionised water (3 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography. Elution with 70% ethyl acetate/light petroleum afforded *rac*-**142** as a colourless oil (1.13 g, 63%). The oil was diluted with anhydrous dichloromethane (60 mL) and stirred with activated manganese dioxide (6.90 g, 0.08 mol, 10.0 eq.) at room temperature for 3 days. The reaction mixture was filtered and the filtrate concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography. Elution with 30% ethyl acetate/light petroleum afforded the ketone **145** as a yellow oil (779 mg, 70%). The spectroscopic data matched that reported in the literature.²¹⁷

^1H NMR (400 MHz, CDCl_3): δ 3.39 (1 H, br. s), 2.51 (2 H, q, $J = 7.4$ Hz), 1.50 (6 H, s), 1.07 (3 H, t, $J = 7.4$ Hz) ppm.

9.3.9 Asymmetric reduction of the ketone **145**

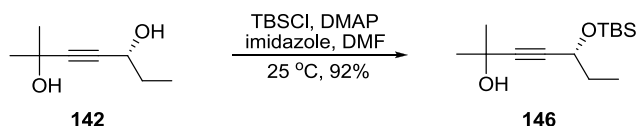


(*S*)-(-)-2-Methyl-CBS-oxazaborolidine (119 mg, 0.43 mmol, 10 mol%) was added to a solution of $\text{BH}_3\cdot\text{DMS}$ (650 mg, 0.81 mL, 8.56 mmol, 2.0 eq.) in anhydrous tetrahydrofuran (10 mL) and stirred at room temperature for 15 minutes. The solution was cooled to 0°C and the ketone **145** (600 mg, 4.28 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (10 mL) was added dropwise over 2 hours. The reaction mixture was stirred for a further hour. Methanol (6 mL) was then added at 0°C followed by a saturated aqueous solution of NH_4Cl (5 mL). The mixture was diluted with dichloromethane (15 mL) and the organic layer extracted. The organic layer was dried and the solvent removed under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography. Elution with 70% ethyl

acetate/light petroleum afforded the diol **142** as a colourless oil (517 mg, 85%) in 96% *ee*. The spectroscopic data matched that reported in the literature.²¹⁷

¹H NMR (400 MHz, CDCl₃) δ 4.33 (1 H, t, J = 6.5 Hz), 2.24 (2 H, br. s), 1.73 (2 H, m), 1.51 (6 H, s), 0.99 (3 H, t, J = 7.4 Hz) ppm; $[\alpha]_D^{20}$ = -3.11 (c = 1.00, CH₃OH).

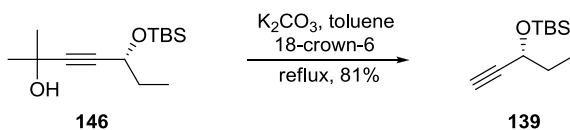
9.3.10 Monosilylation of the diol **142**



A mixture of the diol **142** (330 mg, 2.32 mmol, 1.0 eq.), imidazole (237 mg, 3.48 mmol, 1.5 eq.) and DMAP (28 mg, 0.23 mmol, 0.1 eq.) in anhydrous dichloromethane (7 mL) was stirred for 10 minutes at 0 °C. TBSCl (350 mg, 2.32 mmol, 1.0 eq.) was added in small portions and the mixture was allowed to warm to room temperature and stirred for 24 hours. The resulting mixture was diluted with ethyl acetate (10 mL), washed with an aqueous CuSO₄ solution (2 mL) and washed with deionised water (2 x 10 mL). The organic layer was dried and concentrated under reduced pressure. The resulting oil was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 30% ethyl acetate/light petroleum afforded compound **146** as a colourless oil (548 mg, 92%).

¹H NMR (400 MHz, CDCl₃): δ 4.29 (1 H, t, J = 6.4 Hz), 1.89 (1 H, br. s), 1.65 (2 H, m), 1.50 (6 H, s), 0.94 (3 H, t, J = 7.4 Hz), 0.90 (9 H, s), 0.12 (3 H, s), 0.10 (3 H, s) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 88.7 (C), 83.9 (C), 65.3 (C), 64.3 (CH), 31.9 (CH₂), 31.6 (CH₃), 31.5 (CH₃), 26.0 (CH₃), 18.4 (C), 9.9 (CH₃), -4.3 (CH₃), -4.8 (CH₃) ppm; **ATR-FTIR**: 3352 (OH) cm⁻¹; **HRMS (ASAP)**: $[M-H_2O]^+$ C₁₄H₂₈O₂Si requires 239.1831; found: 239.1829; $[\alpha]_D^{25}$ = -16.20 (c = 1.00, CH₃OH).

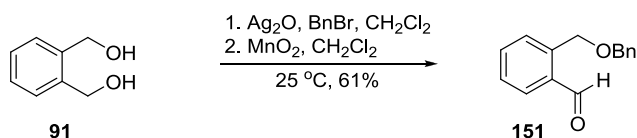
9.3.11 Preparation of the alkyne **139**



Following the same procedure as Boyall et al.,²¹⁶ a mixture of the alcohol **146** (590 mg, 2.30 mmol, 1.0 eq.), K₂CO₃ (318 mg, 2.30 mmol, 1.0 eq.) and 18-crown-6 (608 mg, 2.30 mmol, 1.0 eq.) in toluene (6 mL) was heated under reflux for 5 hours. The solvent was removed under reduced pressure and the mixture diluted with ether (2 mL). The ethereal solution was washed with deionised water (5 x 3 mL), dried and concentrated under reduced pressure. The resulting oil was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with light petroleum afforded the alkyne **139** as a colourless oil (370 mg, 81%). The spectroscopic data matched that reported in the literature.²¹¹

¹H NMR (400 MHz, CDCl₃): δ 4.27 (1 H, t, *J* = 6.3 Hz), 2.35 (1 H, s), 1.68 (2 H, m), 0.96 (3 H, t, *J* = 7.4 Hz), 0.89 (9 H, s), 0.12 (3 H, s), 0.10 (3 H, s) ppm; [α]_D²⁵ = −0.40 (*c* = 1.00, CH₃Cl).

9.3.12 Preparation of the aldehyde **151**

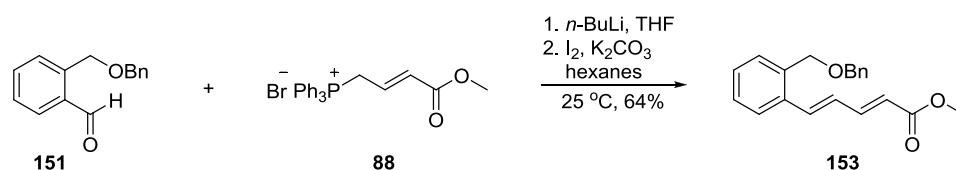


A mixture of the diol **91** (4.24 g, 30.69 mmol, 1.0 eq.), silver oxide (10.67 g, 46.03 mmol, 1.5 eq.) and benzyl bromide (5.77 g, 33.76 mmol, 1.1 eq.) in anhydrous dichloromethane (100 mL) was stirred for 6 hours at room temperature. The reaction mixture was filtered and the solvent removed under reduced pressure to give a brown liquid. The liquid was subjected to column chromatography. Elution with 40% ethyl acetate/light petroleum afforded the alcohol **152** as a light brown oil (6.09 g, 87%). The oil was redissolved in anhydrous dichloromethane (180 mL). Activated manganese dioxide (26.68 g, 0.31 mol, 10.0 eq.) was added and the mixture was stirred at room temperature for 3 days. The reaction mixture was filtered and the solvent removed under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography. Elution with 10% ethyl acetate/light petroleum

afforded the aldehyde **151** as a yellow oil (4.86 g, 70%). The ^1H NMR spectrum matched the spectrum reported in the literature.³⁰⁸

^1H NMR (400 MHz, CDCl_3): δ 10.23 (1 H, s), 7.87 (1 H, d, $J = 7.6$ Hz), 7.70 (1 H, d, $J = 7.6$ Hz), 7.61 (1 H, dd, $J = 7.6, 7.6$ Hz), 7.48 (1 H, dd, $J = 7.6, 7.6$ Hz), 7.25–7.45 (5 H, m), 4.99 (2 H, s), 4.67 (2 H, s) ppm.

9.3.13 Synthesis of the ester **153**

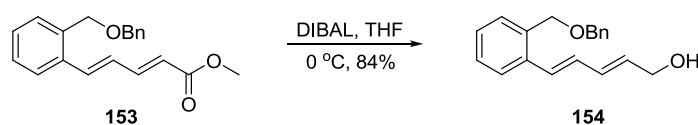


$n\text{-BuLi}$ (1.6 M in hexanes, 1.66 mL, 2.65 mmol, 1.2 eq.) was added dropwise to the phosphonium salt **88** (1.07 g, 2.43 mmol, 1.1 eq.) in anhydrous tetrahydrofuran (15 mL) at 0 °C. The reaction mixture was stirred for 20 minutes at 0 °C and allowed to warm to room temperature over 10 minutes. Compound **151** (500 mg, 2.21 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (10 mL) was added dropwise to the solution at room temperature and the resulting mixture was stirred for 17 hours. The mixture was dried and concentrated under reduced pressure to afford an orange liquid. The liquid was subjected to column chromatography. Elution with 10% ethyl acetate/light petroleum gave an orange oil as a 1:1 mixture of $2E,4E:2E,4Z$ isomers (538 mg, 79%). The oil (538 mg, 1.75 mmol, 1.0 eq.) was then dissolved in hexane (285 mL) and stirred with iodine (155 mg, 1.22 mmol, 0.7 eq.) and anhydrous potassium carbonate (1.21 g, 8.73 mmol, 5.0 eq.) at room temperature for two and a half hours. The reaction mixture was filtered and the filtrate washed with a solution of sodium metabisulfite (5% aq., 2 x 30 mL) and deionised water (30 mL). The organic layer was dried and concentrated under reduced pressure to afford the $2E,4E$ -isomer of **153** as a yellow oil (436 mg, 81%). The ^1H NMR spectrum of the crude sample showed no $2E,4Z$ -isomer.

^1H NMR (400 MHz, CDCl_3): δ 7.61 (1 H, d, $J = 6.9$ Hz), 7.26–7.48 (9 H, m), 7.18 (1 H, d, $J = 15.5$ Hz), 6.83 (1 H, dd, $J = 11.1, 15.5$ Hz), 6.00 (1 H, d, $J = 15.3$ Hz), 4.59 (2 H, s), 4.50 (2 H, s), 3.80 (3 H, s) ppm; ^{13}C NMR (100 MHz, CDCl_3):

δ 167.6 (C), 145.2 (CH), 138.0 (C), 137.7 (CH), 136.1 (C), 135.5 (C), 130.1 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 126.1 (CH), 121.1 (CH), 72.5 (CH₂), 70.1 (CH₂), 51.7 (CH₃) ppm; **ATR-FTIR**: 1713 (C=O) cm⁻¹; **HRMS (ASAP)**: [M⁺] C₂₀H₂₀O₃ requires 309.1491; found: 309.1487.

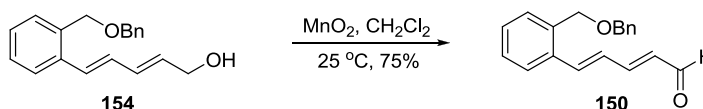
9.3.14 Reduction of the ester **153**



DIBAL (1 M in toluene, 10.76 mL, 10.76 mmol, 2.1 eq.) was added dropwise to the ester **153** (1.58 g, 5.12 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (112 mL) at 0 °C. The mixture was stirred for 2 hours while maintaining the temperature. A saturated aqueous solution of sodium sulfate (40 mL) was added dropwise to the reaction mixture, resulting in a fine suspension. The suspension was filtered and the filtrate was dried and concentrated under reduced pressure to give an orange liquid. The liquid was subjected to column chromatography. Elution with 30% ethyl acetate/light petroleum afforded the alcohol **154** as an orange oil (1.21 g, 84%).

¹H NMR (400 MHz, CDCl₃): δ 7.56 (1 H, d, J = 7.7 Hz), 7.22–7.44 (8 H, m), 6.85 (1 H, d, J = 15.5 Hz), 6.72 (1 H, dd, J = 10.2, 15.5 Hz), 6.42 (1 H, dd, J = 10.2, 15.2 Hz), 5.96 (1 H, dt, J = 5.9, 15.2 Hz), 4.60 (2 H, s), 4.57 (2 H, s), 4.25 (2 H, d, J = 5.9 Hz) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 138.3 (C), 136.6 (C), 135.2 (C), 132.8 (CH), 132.0 (CH), 130.1 (CH), 129.8 (CH), 129.8 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 125.7 (CH), 72.3 (CH₂), 70.4 (CH₂), 63.5 (CH₂) ppm; **ATR-FTIR**: 3385 (OH) cm⁻¹; **HRMS (ASAP)**: [M⁺] C₂₀H₁₉O₂ requires 280.1464; found: 280.1463.

9.3.15 Oxidation of the alcohol **154**

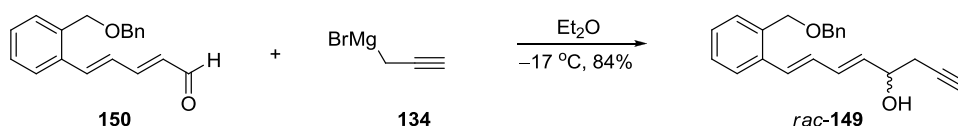


A mixture of the alcohol **154** (1.20 g, 4.28 mmol, 1.0 eq.) and activated manganese dioxide (3.72 g, 42.80 mmol, 10.0 eq.) in anhydrous dichloromethane (80 mL) was stirred at room temperature for 24 hours. The reaction mixture was filtered and the

filtrate concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 20% ethyl acetate/light petroleum afforded the aldehyde **150** as a yellow oil (894 mg, 75%).

^1H NMR (400 MHz, CDCl_3): δ 9.50 (1 H, d, $J = 7.9$ Hz), 7.61 (1 H, d, $J = 8.9$ Hz), 7.21–7.27 (9 H, m), 7.05 (1 H, dd, $J = 10.9, 15.2$ Hz), 6.81 (1 H, dd, $J = 10.9, 15.4$ Hz), 6.15 (1 H, dd, $J = 7.9, 15.2$ Hz), 4.51 (2 H, s), 4.46 (2 H, s) ppm; **^{13}C NMR** (100 MHz, CDCl_3): δ 193.5 (C), 152.3 (CH), 139.7 (CH), 137.9 (C), 136.3 (C), 135.0 (C), 131.7 (CH), 130.2 (CH), 129.3 (CH), 128.5 (CH), 128.5 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 126.2 (CH), 72.2 (CH_2), 70.1 (CH_2) ppm; **ATR-FTIR**: 1674 ($\text{C}=\text{O}$) cm^{-1} ; **HRMS (ASAP)**: $[\text{M}^+]$ $\text{C}_{19}\text{H}_{18}\text{O}_2$ requires 279.1385; found: 279.1399.

9.3.16 Propargylation of the aldehyde **150**

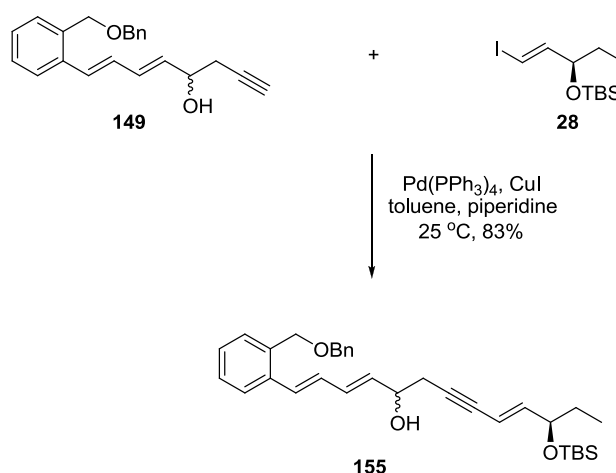


Propargyl bromide (80% w/v in toluene, 118 mg, 0.79 mmol, 1.1 eq.) was added in one portion to a mixture of magnesium turnings (38 mg, 1.58 mmol, 2.0 eq.), iodine (5 mg, 0.04 mmol) and HgCl_2 (10 mg, 0.04 mmol) in anhydrous ether (1 mL) at 0 °C. The reaction mixture was stirred for 20 minutes at 0 °C then cooled to -17 °C. Compound **150** (200 mg, 0.72 mmol, 1.0 eq.) in anhydrous ether (4 mL) was added dropwise at -17 °C and the mixture was stirred for two and a half hours. The mixture was warmed to 0 °C and a saturated aqueous solution of NH_4Cl (3 mL) was added dropwise. The mixture was diluted with ether (15 mL) and washed with deionised water (2 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 30% ethyl acetate/light petroleum afforded *rac*-**149** as a yellow oil (192 mg, 84%).

^1H NMR (400 MHz, CDCl_3): δ 7.56 (1 H, d, $J = 7.7$ Hz), 7.23–7.45 (8 H, m), 6.87 (1 H, d, $J = 15.5$ Hz), 6.72 (1 H, dd, $J = 10.4, 15.5$ Hz), 6.46 (1 H, dd, $J = 10.4, 15.2$ Hz), 5.90 (1 H, $J = 6.3, 15.2$ Hz), 4.60 (2 H, s), 4.57 (2 H, s), 4.42 (1 H, m),

2.54 (1 H, ddd, $J = 2.6, 5.5, 16.7$ Hz), 2.50 (1 H, ddd, $J = 2.6, 5.5, 16.7$ Hz), 2.15 (1 H, br. s), 2.10 (1 H, t, $J = 2.6$ Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 138.3 (C), 136.5 (C), 135.2 (C), 134.2 (CH), 132.1 (CH), 130.5 (CH), 129.9 (CH), 129.8 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 125.7 (CH), 80.4 (CH), 72.3 (CH_2), 71.2 (C), 70.5 (CH), 70.3 (CH_2), 27.8 (CH_2) ppm; ATR-FTIR: 3390 (OH) cm^{-1} ; HRMS (ESI): $[\text{M}+23(\text{Na})]^+$ $\text{C}_{22}\text{H}_{22}\text{O}_2$ requires 341.1517; found: 341.1514.

9.3.17 Sonogashira reaction between *rac*-**149** and compound **28**

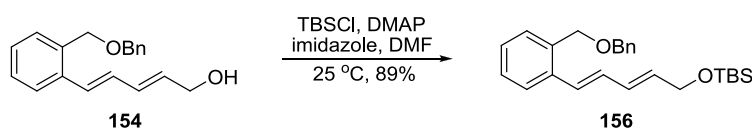


Compound **28** (360 mg, 1.10 mmol, 1.0 eq.), $\text{Pd(PPh}_3)_4$ (89 mg, 0.08 mmol, 7 mol%), CuI (21 mg, 0.11 mmol, 10 mol%), piperidine (188 mg, 2.21 mmol, 2.0 eq.) and BHT (1 crystal) were added in one portion to the alkyne **149** (351 mg, 1.10 mmol, 1.0 eq.) in degassed anhydrous toluene (1 mL) and the mixture was stirred for 12 hours at room temperature. The mixture was diluted with ether (10 mL) and washed with deionised water (3 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 30% ethyl acetate/light petroleum afforded compound **155** as a yellow oil (473 mg, 83%).

^1H NMR (400 MHz, CDCl_3): δ 7.55 (1 H, dd, $J = 1.4, 7.7$ Hz), 7.24–7.36 (8 H, m), 6.85 (1 H, d, $J = 15.5$ Hz), 6.71 (1 H, dd, $J = 10.6, 15.5$ Hz), 6.46 (1 H, dd, $J = 10.6, 15.3$ Hz), 6.09 (1 H, dd, $J = 5.4, 15.8$ Hz), 5.90 (1 H, dd, $J = 6.3, 15.3$ Hz), 5.65 (1 H, dt, $J = 1.6, 15.8$ Hz), 4.59 (2 H, s), 4.57 (2 H, s), 4.40 (1 H, m), 4.10 (1 H, m), 2.67 (1 H, ddd, $J = 1.6, 6.3, 16.7$ Hz), 2.60 (1 H, ddd, $J = 1.6, 6.3, 16.7$ Hz), 2.13 (1

H, br. s), 1.51 (2 H, m), 0.90 (9 H, s), 0.87 (3 H, t, $J = 7.5$ Hz), 0.05 (6 H, s) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 146.2 (CH), 138.3 (C), 136.6 (C), 135.2 (C), 134.6 (CH), 131.9 (CH), 130.3 (CH), 130.0 (CH), 129.8 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 125.7 (CH), 108.7 (CH), 85.6 (C), 81.8 (C), 73.7 (CH), 72.4 (CH_2), 70.8 (CH), 70.3 (CH_2), 30.8 (CH_2), 29.0 (CH_2), 26.0 (CH_3), 18.4 (C), 9.4 (CH_3), -4.4 (CH_3), -4.7 (CH_3) ppm; ATR-FTIR: 3400 (OH) cm^{-1} , HRMS (ESI): $[\text{M}+23 (\text{Na})]^+$ $\text{C}_{33}\text{H}_{44}\text{O}_3\text{Si}$ requires 539.2957; found: 539.2976.

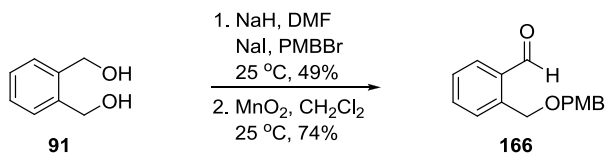
9.3.18 Silylation of the alcohol **154**



A mixture of the alcohol **154** (510 mg, 1.82 mmol, 1.0 eq.), imidazole (186 mg, 2.73 mmol, 1.5 eq.) and DMAP (22 mg, 0.18 mmol, 0.1 eq.) in anhydrous dimethylformamide (7 mL) was stirred at 0 °C for 10 minutes. TBSCl (274 mg, 0.18 mol, 1.0 eq.) was added in portions and the mixture was allowed to warm to room temperature and stirred for 11 hours. The reaction mixture was diluted with ether (15 mL), washed with an aqueous CuSO_4 solution (5 mL) and washed with deionised water (2 x 15 mL). The organic layer was dried and concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with light petroleum afforded compound **156** as a colourless oil (639 mg, 89%).

^1H NMR (400 MHz, CDCl_3): δ 7.44 (1 H, d, $J = 7.0$ Hz), 7.03–7.26 (8 H, m), 6.85 (1 H, d, $J = 15.5$ Hz), 6.76 (1 H, dd, $J = 10.0, 15.5$ Hz), 6.31 (1 H, dd, $J = 10.0, 15.1$ Hz), 5.78 (1 H, dt, $J = 5.2, 15.1$ Hz), 4.49 (2 H, s), 4.45 (2 H, s), 4.17 (2 H, d, $J = 5.2$ Hz), 0.83 (9 H, s), 0.00 (6 H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 138.4 (C), 136.9 (C), 135.1 (C), 133.8 (CH), 130.7 (CH), 130.4 (CH), 129.7 (CH), 128.8 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.4 (CH), 125.7 (CH), 72.3 (CH_2), 70.4 (CH_2), 63.8 (CH_2), 26.1 (CH_3), 18.6 (C), -5.0 (CH_3) ppm; HRMS (ASAP): $[\text{M}^+]$ $\text{C}_{26}\text{H}_{36}\text{O}_3\text{Si}$ requires 395.2406; found: 395.2423.

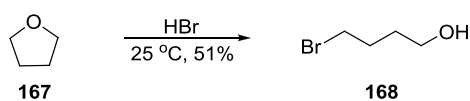
9.3.19 Preparation of the aldehyde **166**



60% NaH in mineral oil (1.75 g, 43.77 mmol, 1.4 eq.) was added in portions to a mixture of the diol **91** (4.32 g, 31.27 mmol, 1.0 eq.) and NaI (234 mg, 1.56 mmol) in anhydrous dimethylformamide (60 mL) at 0 °C. The mixture was stirred for 30 minutes followed by dropwise addition of *p*-methoxybenzyl bromide (6.92 g, 34.39 mmol, 1.1 eq.). The mixture was allowed to warm to room temperature and stirred for a further 16 hours. The reaction was quenched with a saturated aqueous solution of NH₄Cl (20 mL) and the mixture stirred for 30 minutes. The reaction mixture was diluted with ether (120 mL), washed with an aqueous CuSO₄ solution (10 mL), washed with deionised water (2 x 60 mL), dried and concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography. Elution with 40% ethyl acetate/light petroleum afforded the alcohol **165** as a yellow oil (3.96 g, 49%). The oil was redissolved in anhydrous dichloromethane (120 mL) and treated with activated manganese dioxide (13.32 g, 0.15 mol, 10.0 eq.). The reaction mixture was stirred at room temperature for 2 days. After this time, the mixture was filtered and the solvent removed under reduced pressure to give the aldehyde **166** as a yellow oil (3.93 g, 74%). The ¹H NMR spectrum matched the spectrum reported in the literature.²³⁵

¹H NMR (400 MHz, CDCl₃): δ 10.22 (1 H, s), 7.87 (1 H, dd, *J* = 7.4, 7.8 Hz), 7.67 (1 H, d, *J* = 7.4 Hz), 7.59 (1 H, d, *J* = 7.4 Hz), 7.47 (1 H, dd, *J* = 7.4, 7.8 Hz), 7.31 (2 H, d, *J* = 8.8 Hz), 6.90 (2 H, d, *J* = 8.8 Hz), 4.95 (2 H, s), 4.59 (2 H, s), 3.81 (3 H, s) ppm.

9.3.20 Acid-catalysed synthesis of 4-bromo-1-butanol

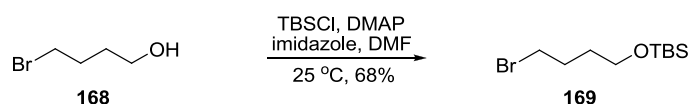


Following the procedure by Supuran and co-workers,³⁰⁹ HBr (48%, 233.77 g, 1.39 mol, 1.0 eq.) was added dropwise to tetrahydrofuran (100 g, 1.39 mol, 1.0 eq.)

at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 5 hours. The mixture was cooled to 0 °C and diluted with dichloromethane (150 mL). A saturated aqueous solution of sodium hydroxide (50 mL) was then added dropwise. The organic layer was washed with deionised water (2 x 50 mL), dried and concentrated under reduced pressure to give 4-bromo-1-butanol as a yellow oil (108.23 g, 51%). The ^1H NMR spectrum matched that reported in the literature.²³⁶

^1H NMR (400 MHz, CDCl_3): δ 3.67 (2 H, t, J = 6.4 Hz), 3.44 (2 H, t, J = 6.7 Hz), 2.43 (1 H, br. s), 1.94 (2 H, m), 1.70 (2 H, m) ppm.

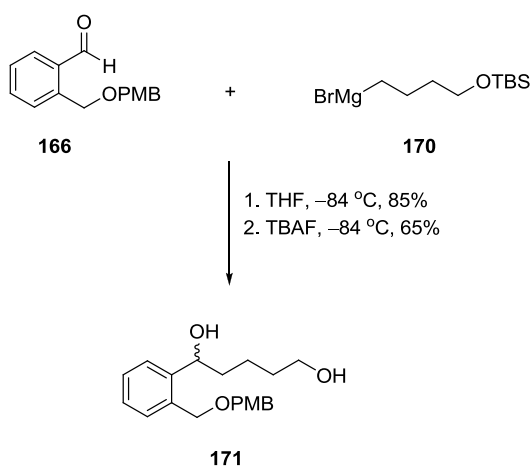
9.3.21 Silylation of 4-bromo-1-butanol



A mixture of 4-bromo-1-butanol (15.30 g, 0.1 mol, 1.0 eq.), imidazole (10.21 g, 0.15 mol, 1.5 eq.) and DMAP (1.22 g, 0.01 mol, 0.1 eq.) in anhydrous dimethylformamide (50 mL) was stirred at 0 °C for 10 minutes. TBSCl (15.07 g, 0.1 mol, 1.0 eq.) was added in portions and the mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with ether (100 mL), washed with an aqueous CuSO_4 solution (5 mL) and washed with deionised water (2 x 30 mL). The organic layer was dried and concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with light petroleum afforded the bromide **169** as a colourless oil (18.17 g, 68%). The ^1H NMR spectrum matched that in the literature.²³⁷

^1H NMR (400 MHz, CDCl_3): δ 3.64 (2 H, t, J = 6.2 Hz), 3.44 (2 H, t, J = 6.8 Hz), 1.94 (2 H, m), 1.65 (2 H, m), 0.89 (9 H, s), 0.04 (6 H, s) ppm.

9.3.22

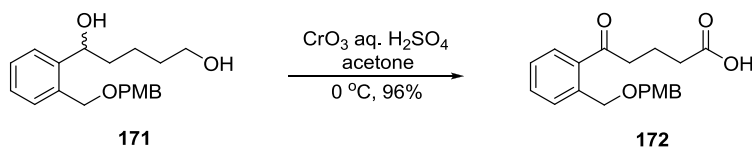
Addition of the Grignard reagent **170** to compound **166**

A mixture of the bromide **169** (7.19 g, 26.88 mmol, 2.6 eq.) and magnesium turnings (1.26 g, 51.70 mmol, 5.0 eq.) in anhydrous tetrahydrofuran (26 mL) was stirred at room temperature for 10 minutes with gradual addition of 1,2-dibromoethane (194 mg, 1.03 mmol, 0.1 eq.). The reaction mixture was warmed to 45 °C upon initiation and stirred for 3 hours. After this time, the mixture was cooled to -84 °C and the aldehyde **166** (2.65 g, 0.01 mol, 1.0 eq.) was added dropwise. The reaction mixture was stirred for a further 2 hours. A saturated aqueous solution of NH₄Cl (10 mL) was then added dropwise at 0 °C. The mixture was diluted with dichloromethane (30 mL) and washed with deionised water (2 x 20 mL). The organic layer was dried and concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography. Elution with 5% ethyl acetate/light petroleum afforded the silyl protected ether **171** as a yellow oil (3.91 g, 85%). The oil (396 mg, 0.89 mmol, 1.0 eq.) was taken up in anhydrous tetrahydrofuran (5 mL) and added dropwise to a solution of TBAF (1 M in tetrahydrofuran, 1.07 mL, 1.07 mmol, 1.2 eq.) at -84 °C. The mixture was allowed to gradually warm to room temperature over 22 hours. The mixture was then concentrated under reduced pressure to give a yellow liquid that was subjected to column chromatography. Elution with 70% ethyl acetate/light petroleum afforded the diol **171** as a colourless oil (191 mg, 65%).

¹H NMR (400 MHz, CDCl₃): δ 7.48 (1 H, d, *J* = 7.5 Hz), 7.38 (1 H, dd, *J* = 7.5, 7.8 Hz), 7.24–7.30 (4 H, m), 6.88 (2 H, d, *J* = 8.8 Hz), 4.87 (1 H, dd, *J* = 4.8, 8.4 Hz), 4.65 (1 H, d, *J* = 11.2 Hz), 4.49 (2 H, s), 4.48 (1 H, d, *J* = 11.2 Hz), 3.80 (3 H, s), 3.58 (2 H, t, *J* = 6.3 Hz), 2.41 (2 H, s), 1.85 (1 H, m), 1.74 (1 H, m), 1.50–1.72 (3

H, m), 1.38 (1 H, m) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 159.5 (C), 144.0 (C), 134.9 (C), 130.3 (CH), 129.8 (CH), 129.8 (C), 129.0 (CH), 127.5 (CH), 126.3 (CH), 114.0 (CH), 72.3 (CH_2), 70.6 (CH_2), 70.4 (CH), 62.8 (CH_2), 55.4 (CH_3), 36.8 (CH_2), 32.6 (CH_2), 22.7 (CH_2) ppm; ATR-FTIR: 3385 (2 x OH) cm^{-1} ; HRMS (ESI): $[\text{M}+23 (\text{Na})]^+$ $\text{C}_{20}\text{H}_{26}\text{O}_4$ requires 353.1729; found: 353.1731.

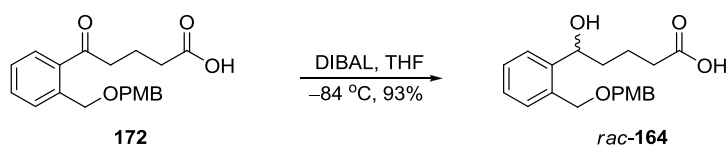
9.3.23 Oxidation of the diol **171** with Jones reagent



Jones reagent (1 M, 0.95 mL, 0.95 mmol, 3.4 eq.) was added dropwise to a solution of the diol **171** (92 mg, 0.28 mmol, 1.0 eq.) in acetone (30 mL) at 0 °C and the mixture was stirred for four and a half hours. Methanol (2 mL) was then added dropwise at this temperature, resulting in a suspension. The suspension was filtered and the filtrate diluted with ethyl acetate (60 mL). The reaction mixture was washed with deionised water (10 mL) and brine (2 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give the ketoacid **172** as a white solid (92 mg, 96%); m.p. 67–68 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.65 (2 H, d, $J = 7.7$ Hz), 7.48 (1 H, dd, $J = 7.7$, 7.8 Hz), 7.25–7.30 (3 H, m), 6.88 (2 H, d, $J = 8.6$ Hz), 4.80 (2 H, s), 4.52 (2 H, s), 3.80 (3 H, s), 2.98 (2 H, t, $J = 7.2$ Hz), 2.43 (2 H, t, $J = 7.2$ Hz), 2.01 (2 H, m) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 203.4 (C), 178.9 (C), 159.4 (C), 139.1 (C), 137.0 (C), 131.7 (CH), 130.4 (C), 129.5 (CH), 128.4 (CH), 128.4 (CH), 127.2 (CH), 113.9 (CH), 72.7 (CH_2), 70.3 (CH_2), 55.4 (CH_3), 40.1 (CH_2), 33.2 (CH_2), 19.2 (CH_2) ppm; ATR-FTIR: 1705 (carboxylic acid: C=O) and 1682 (ketone: C=O) cm^{-1} ; HRMS (ASAP): $[\text{M}-1 (\text{H})]^+$ $\text{C}_{20}\text{H}_{22}\text{O}_5$ requires 341.1389; found: 341.1377.

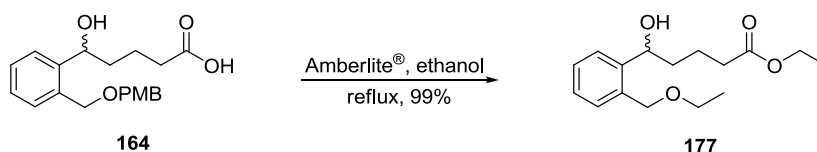
9.3.24 Reduction of the ketone **172**



DIBAL (25% w/v in toluene, 0.32 mL, 0.45 mmol, 2.1 eq.) was added dropwise to the ketoacid **172** (74 mg, 0.22 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (2 mL) at $-84\text{ }^{\circ}\text{C}$. The reaction mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$ and stirred for three and a half hours. Methanol (2 mL) and a saturated aqueous solution of sodium sulfate (2 mL) were added successively, resulting in a fine suspension. The reaction mixture was filtered and the filtrate concentrated under reduced pressure to give *rac*-**164** as a colourless oil (74 mg, 93%).

^1H NMR (400 MHz, CDCl_3): δ 7.44 (1 H, d, $J = 7.2$ Hz), 7.43 (1 H, br. s), 7.16–7.26 (5 H, m), 6.85 (2 H, d, $J = 8.6$ Hz), 4.77 (1 H, m), 4.48 (1 H, d, $J = 11.5$ Hz), 4.43 (1 H, d, $J = 11.5$ Hz), 4.37 (2 H, s), 3.77 (3 H, s), 2.28 (2 H, m), 1.93 (2 H, m), 1.72 (2 H, m) ppm; **^{13}C NMR** (100 MHz, CDCl_3): δ 180.1 (C), 159.3 (C), 144.0 (C), 134.3 (C), 130.1 (C), 129.6 (CH), 129.4 (CH), 128.4 (CH), 127.0 (CH), 126.1 (CH), 113.9 (CH), 71.9 (CH_2), 69.7 (CH_2), 69.6 (CH), 55.3 (CH_3), 37.8 (CH_2), 35.8 (CH_2), 22.3 (CH_2) ppm; **ATR-FTIR**: 3390 (OH) and 1681 ($\text{C}=\text{O}$) cm^{-1} ; **HRMS (ASAP)**: $[\text{M}^+]$ $\text{C}_{20}\text{H}_{24}\text{O}_5$ requires 345.1702; found: 345.1704.

9.3.25 Acid-catalysed esterification of compound **164**

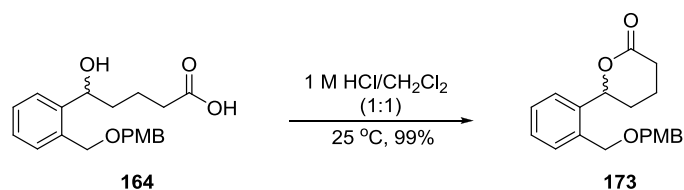


A mixture of compound **164** (15 mg, 0.04 mmol, 1.0 eq.), Amberlite[®] IR-120 (4 crystals) and crushed 3Å molecular sieves (2 sieves) in anhydrous ethanol (3 mL) was heated under reflux for 5 hours. Amberlite[®] IR-120 and 3Å molecular sieves were removed by filtration and the filtrate was concentrated under reduced pressure to afford compound **177** as a yellow oil (12 mg, 99%).

^1H NMR (400 MHz, CDCl_3): δ 7.38 (1 H, dd, $J = 1.7, 7.7$ Hz), 7.34 (1 H, dd, $J = 1.7, 7.0$ Hz), 7.31 (1 H, dd, $J = 1.7, 7.7$ Hz), 7.28 (1 H, dd, $J = 1.7, 7.0$ Hz), 4.78 (1

H, d, $J = 12.5$ Hz), 4.68 (1 H, d, $J = 12.5$ Hz), 4.55 (1 H, dt, $J = 4.7, 8.1$ Hz), 4.11 (2 H, q, $J = 7.1$ Hz), 3.36 (2 H, m), 2.51 (1 H, br. s), 2.32 (2 H, m), 1.86 (2 H, m), 1.71 (2 H, m), 1.24 (3 H, t, $J = 7.1$ Hz), 1.17 (3 H, t, $J = 7.0$ Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 173.8 (C), 141.0 (C), 138.5 (C), 129.4 (CH), 128.3 (CH), 127.8 (CH), 127.5 (CH), 79.6 (CH), 64.4 (CH_2), 63.5 (CH_2), 60.4 (CH_2), 36.6 (CH_2), 34.2 (CH_2), 21.9 (CH_2), 15.5 (CH_3), 14.4 (CH_3) ppm; **HRMS (ESI)**: Molecular ion not found

9.3.26 Acid-catalysed lactonisation of compound **164**

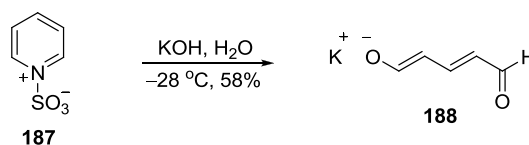


A mixture of compound **164** (32 mg, 0.09 mmol, 1.0 eq.), 1 M HCl (2 mL) and dichloromethane (2 mL) was stirred at room temperature for 19 hours. The organic layer was extracted with dichloromethane (2 x 10 mL) and the solvent removed under reduced pressure to give the lactone **173** (30 mg, 99%) as a colourless oil. Attempts to purify the product via column chromatography proved unsuccessful.

^1H NMR (400 MHz, CDCl_3): δ 7.47 (1 H, d, $J = 7.6$ Hz), 7.24–7.47 (4 H, m), 6.90 (3 H, d, $J = 8.7$ Hz), 5.56 (1 H, dd, $J = 3.1, 11.0$ Hz), 4.65 (1 H, d, $J = 11.4$ Hz), 4.47 (3 H, m), 3.81 (3 H, s), 2.64 (1 H, m), 2.57 (1 H, m), 2.11 (1 H, m), 1.93 (3 H, m) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 171.8 (C), 159.5 (C), 139.2 (C), 134.4 (C), 130.1 (CH), 130.0 (C), 129.8 (CH), 128.9 (CH), 128.2 (CH), 126.8 (CH), 114.0 (CH), 78.5 (CH), 72.0 (CH_2), 70.1 (CH_2), 55.4 (CH_3), 30.6 (CH_2), 29.5 (CH_2), 19.0 (CH_2) ppm; **ATR-FTIR**: 1731 (C=O) cm^{-1} .

9.4 Chapter 4 experimental procedures

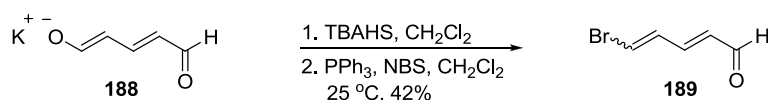
9.4.1 Synthesis of potassium glutaconaldehyde **188**



Following the procedure outlined by Becher,²³⁹ pyridinium sulfonic acid (12.03 g, 0.08 mol, 1.0 eq.) was added in small portions to a solution of potassium hydroxide (17.39 g, 0.31 mol, 4.1 eq.) in deionised water (110 mL) at $-28\text{ }^{\circ}\text{C}$. The mixture was gradually warmed to room temperature and stirred for 3 hours and then heated to $39\text{ }^{\circ}\text{C}$ and stirred for a further 30 minutes. The reaction mixture was cooled to $0\text{ }^{\circ}\text{C}$ to precipitate compound **188** as light brown prisms (5.97 g, 58%). The ^1H NMR spectrum of the product matched the spectrum provided by Becher.²³⁹

^1H NMR (400 MHz, DMSO): δ 8.64 (1 H, d, $J = 9.2$ Hz), 7.04 (2 H, t, $J = 13.1$ Hz), 5.11 (2 H, m) ppm.

9.4.2 Synthesis of the bromide **189**

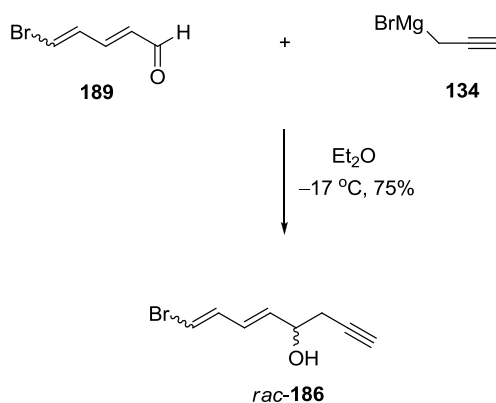


Tetrabutylammonium hydrogen sulfate (1.94 g, 5.73 mmol, 1.0 eq.) was added in one portion to compound **188** (0.78 g, 5.73 mmol, 1.0 eq.) in deionised water (12 mL) at $0\text{ }^{\circ}\text{C}$. The mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was then basified to pH 10 with NaOH (1 M, 10 mL) and extracted with dichloromethane (3 x 20 mL). The organic layer was dried and the solvent removed under reduced pressure to afford tertbutylammonium glutaconaldehyde as a light pink solid in a quantitative yield (1.94 g). The solid (300 mg, 0.84 mmol, 1.0 eq.) was dissolved in anhydrous dichloromethane (10 mL) and treated with triphenylphosphine (209 mg, 0.80 mmol, 0.9 eq.) and *N*-bromosuccinimide (173 mg, 0.97 mmol, 1.1 eq.). The mixture was stirred at room temperature for 8 hours after which it was diluted with dichloromethane (20 mL) and washed with deionised water (3 x 10 mL). The organic layer was dried and concentrated under reduced pressure to afford a yellow solid. The solid was

subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 20% ethyl acetate/light petroleum afforded the bromide **189** as a red oil in a 1:1 mixture of *2E,4E*:*2E,4Z* isomers (60 mg, 42%). The ^1H NMR spectrum matched that provided by Soullez and co-workers.²³⁸

^1H NMR (400 MHz, CDCl_3): δ 9.64 (1 H, d, $J = 7.9$ Hz, *2E,4Z*), 9.52 (1 H, d, $J = 7.8$ Hz, *2E,4E*), 7.41 (1 H, dd, $J = 10.5, 15.5$ Hz, *2E,4Z*), 6.94–7.03 (3 H, m, *2E,4E*), 6.88 (1 H, dd, $J = 7.1, 10.5$ Hz, *2E,4Z*), 6.71 (1 H, d, $J = 7.1$ Hz, *2E,4Z*), 6.27 (1 H, dd, $J = 7.9, 15.5$ Hz, *2E,4Z*), 6.13 (1 H, dd, $J = 7.8, 15.5$ Hz, *2E,4E*) ppm.

9.4.3 Addition of propargylmagnesium bromide to compound **189**

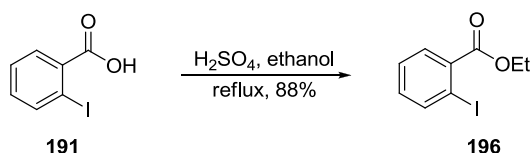


Propargyl bromide (80% w/v in toluene, 137 mg, 0.92 mmol, 1.1 eq.) was added in one portion to a mixture of magnesium turnings (41 mg, 1.68 mol, 2.0 eq.), iodine (5 mg, 0.04 mmol) and HgCl_2 (11 mg, 0.04 mmol) in anhydrous ether (1 mL) at 0 °C. The reaction mixture was stirred for 20 minutes at 0 °C then cooled to –17 °C. Compound **189** (135 mg, 0.84 mmol, 1.0 eq.) in anhydrous ether (2 mL) was added dropwise and the mixture was stirred for two and a half hours. The mixture was warmed to 0 °C and a saturated aqueous solution of NH_4Cl (3 mL) was added dropwise. The mixture was diluted with ether (15 mL) and washed with deionised water (2 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 30% ethyl acetate/light petroleum afforded *rac*-**186** as a yellow oil (126 mg, 75%).

^1H NMR (400 MHz, CDCl_3): δ 6.75 (1 H, dd, $J = 10.8, 13.5$ Hz, *5E,7E*), 6.67 (2 H, m, *5E,7Z*), 6.39 (1 H, d, $J = 13.5$ Hz, *5E,7E*), 6.27 (1 H, dd, $J = 10.8, 15.3$ Hz, *5E,7E*), 6.25 (1 H, m, *5E,7Z*), 6.02 (1 H, m, *5E,7Z*), 5.83 (1 H, dd, $J = 5.9, 15.3$ Hz,

5*E*,7*E*), 4.35 (1 H, m, 5*E*,7*Z*), 4.28 (1 H, m, 5*E*,7*E*), 2.55 (2 H, m, 5*E*,7*Z*), 2.53 (1 H, ddd, $J = 2.7, 5.9, 16.7$ Hz, 5*E*,7*E*), 2.46 (1 H, ddd, $J = 2.7, 5.9, 16.7$ Hz, 5*E*,7*E*), 2.12 (1 H, t, $J = 2.7$ Hz, 5*E*,7*Z*), 2.09 (1 H, t, $J = 2.7$ Hz, 5*E*,7*E*) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 137.8 (CH, 5*E*,7*Z*), 136.6 (CH, 5*E*,7*E*), 134.7 (CH, 5*E*,7*Z*), 131.8 (CH, 5*E*,7*E*), 128.7 (CH, 5*E*,7*E*), 127.0 (CH, 5*E*,7*Z*), 110.0 (CH, 5*E*,7*Z*), 109.5 (CH, 5*E*,7*E*), 80.0 (CH, both isomers), 71.4 (C, both isomers), 70.3 (CH, 5*E*,7*Z*), 70.0 (CH, 5*E*,7*E*), 27.6 (CH_2 , 5*E*,7*Z*), 27.6 (CH_2 , 5*E*,7*E*) ppm; **ATR-FTIR**: 3325 (OH) cm^{-1} ; **Elemental Analysis**: Found: C, 47.74%; H, 4.55%. $\text{C}_8\text{H}_9\text{BrO}$ calculated C, 47.79%; H, 4.51%).

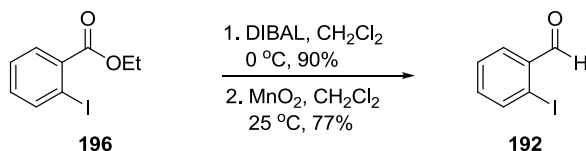
9.4.4 Esterification of *o*-iodobenzoic acid



A mixture of *o*-iodobenzoic acid (6.00 g, 24.19 mmol, 1.0 eq.), concentrated H_2SO_4 (16 mL) and anhydrous ethanol (100 mL) was heated under reflux for 7 hours. The mixture was cooled to 0 °C, quenched with deionised water (60 mL) and extracted with ether (200 mL). The organic layer was dried and the solvent removed under reduced pressure to afford the ester **196** as a colourless oil (5.88 g, 88%). The ^1H NMR spectrum matched the spectrum provided in the literature.³¹⁰

^1H NMR (400 MHz, CDCl_3): δ 7.97 (1 H, d, $J = 7.9$ Hz), 7.78 (1 H, d, $J = 7.9$ Hz), 7.34 (1 H, dd, $J = 7.4, 7.9$ Hz), 7.13 (1 H, dd, $J = 7.4, 7.9$ Hz), 4.39 (2 H, q, $J = 7.2$ Hz), 1.41 (3 H, t, $J = 7.2$ Hz) ppm.

9.4.5 Preparation of *o*-iodobenzaldehyde

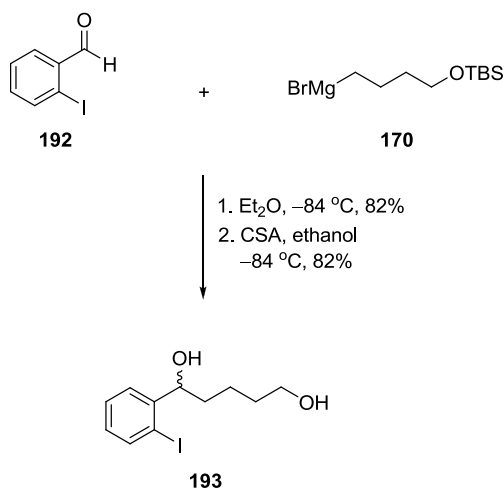


DIBAL (25% w/v in toluene, 31.23 mL, 46.62 mmol, 2.2 eq.) was added dropwise to the ester **196** (5.85 g, 21.19 mmol, 1.0 eq.) in anhydrous dichloromethane (20 mL) at −84 °C. The reaction mixture was allowed to warm to 0 °C and stirred for 4 hours. Methanol (10 mL) and a saturated aqueous solution of sodium sulfate (10 mL) were

added successively, resulting in a fine suspension. The mixture was filtered and the filtrate concentrated under reduced pressure to give *o*-iodobenzyl alcohol as a colourless oil (0.46 g, 90%). The oil was redissolved in anhydrous dichloromethane (50 mL). Activated manganese dioxide (16.58 g, 0.19 mol, 10.0 eq.) was added and the mixture was stirred at room temperature for 2 days. The reaction mixture was filtered and the solvent removed under reduced pressure to give *o*-iodobenzaldehyde as a yellow oil (3.41 g, 77%). The ^1H NMR spectrum matched the spectrum reported in the literature.²⁴¹

^1H NMR (400 MHz, CDCl_3): δ 10.08 (1 H, s), 7.96 (1 H, d, $J = 7.9$ Hz), 7.90 (1 H, d, $J = 7.9$ Hz), 7.48 (1 H, dd, $J = 7.0, 7.9$ Hz), 7.30 (1 H, dd, $J = 7.0, 7.9$ Hz) ppm.

9.4.6 Addition of the Grignard reagent 170 to compound 192

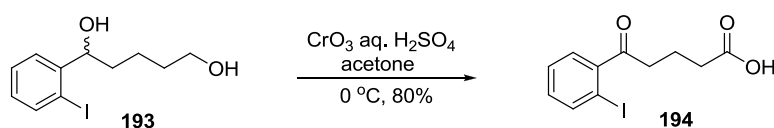


A solution of compound **169** (2.78 g, 10.40 mmol, 1.2 eq.) and magnesium turnings (506 mg, 20.79 mmol, 2.4 eq.) in anhydrous ether (26 mL) was stirred at room temperature for 10 minutes with gradual addition of 1,2-dibromoethane (163 mg, 0.87 mmol, 0.1 eq.). The reaction mixture was heated under reflux upon initiation and stirred for 1 hour. The mixture was cooled to -84°C and *o*-iodobenzaldehyde (2.01 g, 8.66 mmol, 1.0 eq.) in anhydrous ether (10 mL) was added dropwise. The reaction mixture was stirred for 2 hours. A saturated aqueous solution of NH_4Cl (10 mL) was then added dropwise at 0°C . The mixture was diluted with dichloromethane (30 mL) and washed with deionised water (2 x 20 mL). The organic layer was dried and concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography. Elution with 5% ethyl acetate/light petroleum afforded the silylated diol **193** as a yellow oil (2.99 g, 82%). The oil

(2.99 g, 7.10 mmol) was taken up in ethanol (20 mL) and CSA (83 mg, 0.36 mmol) was added. The reaction mixture was stirred at room temperature for 24 hours. The mixture was diluted with ethyl acetate (40 mL) and washed with a saturated aqueous solution of sodium carbonate (10 mL) and deionised water (2 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give the diol **193** as a white solid. The solid was recrystallised from chloroform/light petroleum to give the product as white plates (1.78 g, 82%); m.p. 95–96 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.79 (1 H, d, *J* = 7.9 Hz), 7.50 (1 H, d, *J* = 7.9 Hz), 7.36 (1 H, dd, *J* = 7.7, 7.9 Hz), 6.96 (1 H, dd, *J* = 7.7, 7.9 Hz), 4.90 (1 H, dd, *J* = 3.8, 8.2 Hz), 3.67 (2 H, t, *J* = 6.0 Hz), 1.81 (2 H, br. s), 1.77 (1 H, m), 1.50–1.73 (5 H, m) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 146.7 (C), 139.5 (CH), 129.3 (CH), 128.8 (CH), 127.1 (CH), 97.7 (C), 77.4 (CH), 62.9 (CH₂), 37.6 (CH₂), 32.5 (CH₂), 22.2 (CH₂) ppm; **ATR-FTIR**: 3291 (OH) and 3197 (OH) cm⁻¹; **HRMS (ASAP)**: [M⁺] C₁₁H₁₅IO₂ requires 307.0195; found: 307.0204.

9.4.7 Oxidation of the diol **193** with Jones reagent

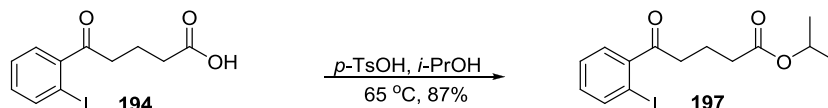


Jones reagent (1.3 M, 9.25 mL, 12.02 mmol, 3.2 eq.) was added dropwise to the diol **193** (1.15 g, 3.76 mmol, 1.0 eq.) in acetone (45 mL) and the mixture was stirred for 4 hours at 0 °C. Methanol was then added dropwise at this temperature, resulting in a suspension. The suspension was filtered and the filtrate diluted with ethyl acetate (60 mL). The reaction mixture was washed with deionised water (10 mL) and brine (2 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give the ketoacid **194** as a white solid which was recrystallised from chloroform/light petroleum as white prisms (956 mg, 80%); m.p. 71–72 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.90 (1 H, d, *J* = 8.0 Hz), 7.30–7.48 (2 H, m), 7.11 (1 H, m), 2.98 (2 H, t, *J* = 7.1 Hz), 2.51 (2 H, t, *J* = 7.1 Hz), 2.07 (2 H, tt, *J* = 7.1, 7.1 Hz) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 204.1 (C), 178.7 (C), 144.6 (C), 140.7 (CH), 131.8 (CH), 128.2 (CH), 127.8 (CH), 91.0 (C), 40.9 (CH₂), 32.9 (CH₂), 19.0

(CH₂) ppm; **ATR-FTIR**: 1702 (carboxylic acid: C=O) and 1688 (ketone: C=O) cm⁻¹; **HRMS (ASAP)**: [M⁺] C₁₁H₁₁IO₃ requires 318.9831; found: 318.9839.

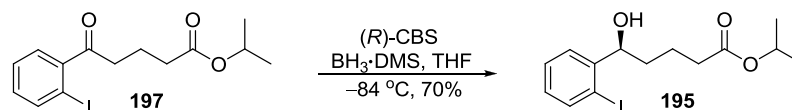
9.4.8 Esterification of the ketoacid **194**



p-Toluenesulfonic acid (60 mg, 0.35 mmol, 0.1 eq.) was added in one portion to the ketoacid **194** (1.11 g, 3.49 mmol, 1.0 eq.) in anhydrous isopropyl alcohol (5 mL) at room temperature. The reaction mixture was heated for 16 hours at 65 °C. The mixture was diluted with dichloromethane (20 mL) and washed with NaHCO₃ (5% aq., 4 mL) and deionised water (2 x 5 mL). The organic layer was dried and concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography. Elution with 10% ethyl acetate afforded the ketoester **197** as a colourless oil (1.09 g, 87%).

¹H NMR (400 MHz, CDCl₃): δ 7.90 (1 H, d, *J* = 7.7 Hz), 7.30–7.47 (2 H, m), 7.11 (1 H, m), 5.00 (1 H, sp, *J* = 6.3 Hz), 2.96 (2 H, t, *J* = 7.2 Hz), 2.40 (2 H, t, *J* = 7.2 Hz), 2.06 (2 H, tt, *J* = 7.2 Hz), 1.23 (6 H, d, *J* = 6.3 Hz) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 204.3 (C), 172.8 (C), 144.8 (C), 140.7 (CH), 131.7 (CH), 128.2 (CH), 127.8 (CH), 91.0 (C), 67.9 (CH), 41.1 (CH₂), 33.7 (CH₂), 22.0 (CH₃), 19.4 (CH₂) ppm; **ATR-FTIR**: 1723 (ester: C=O) and 1699 (ketone: C=O) cm⁻¹; **HRMS (ASAP)**: [M⁺] C₁₄H₁₇IO₃ requires 361.0301; found: 361.0318.

9.4.9 Asymmetric reduction of the ketoester **197**

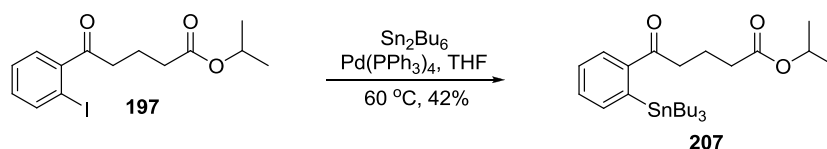


(*R*)-(+)-2-Methyl-CBS-oxazaborolidine (40 mg, 0.14 mmol, 8 mol%) was added to a solution of BH₃•DMS (14 mg, 17.12 μL, 0.18 mmol, 0.1 eq.) in anhydrous tetrahydrofuran (5 mL) and stirred at room temperature for 15 minutes. The solution was cooled to -84 °C and the ketoester **197** (650 mg, 1.80 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (19 mL) was added in one portion followed by dropwise addition of BH₃•DMS (82 mg, 102.69 μL, 1.08 mmol, 0.6 eq.) over 2 hours. The

reaction mixture was stirred for a further 6 hours. Methanol (6 mL) and a saturated aqueous solution of NH_4Cl (8 mL) were then added successively and the mixture was diluted with dichloromethane (30 mL). The organic layer was dried and concentrated under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 20% ethyl acetate/light petroleum afforded the alcohol **195** as a colourless oil (458 mg, 70%) in 94% *ee*.

^1H NMR (400 MHz, CDCl_3): δ 7.77 (1 H, d, $J = 7.8$ Hz), 7.50 (1 H, d, $J = 7.8$ Hz), 7.34 (1 H, dd, $J = 7.7, 7.8$ Hz), 6.94 (1 H, dd, $J = 7.7, 7.8$ Hz), 4.98 (1 H, sp, $J = 6.3$ Hz), 4.85 (1 H, dd, $J = 3.3, 8.8$ Hz), 2.35 (1 H, br. s), 2.34 (2 H, t, $J = 7.0$ Hz), 1.75–1.90 (3 H, m), 1.63 (1 H, m), 1.21 (6 H, d, $J = 6.3$ Hz) ppm; **^{13}C NMR** (100 MHz, CDCl_3): δ 173.4 (C), 146.5 (C), 139.4 (CH), 129.3 (CH), 128.7 (CH), 127.0 (CH), 97.6 (C), 77.0 (CH), 67.8 (CH), 37.3 (CH_2), 34.4 (CH_2), 22.0 (CH_3), 21.3 (CH_2) ppm; **ATR-FTIR**: 3440 (OH) and 1728 ($\text{C}=\text{O}$) cm^{-1} ; $[\alpha]_D^{24} = -41.30^\circ$ ($c = 1.00$, CHCl_3); **HRMS (ESI)**: $[\text{M}+23 (\text{Na})]^+$ $\text{C}_{14}\text{H}_{19}\text{IO}_3$ requires 385.0277; found: 385.0279.

9.4.10 Treatment of hexabutylditin with the ketoester **197**

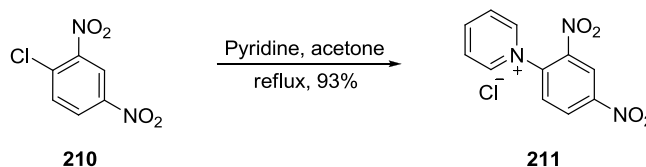


The ketoester **197** (72 mg, 0.20 mmol, 1.0 eq.), $\text{Pd}(\text{PPh}_3)_4$ (32 mg, 0.02 mmol, 2 x 7 mol%) and hexabutylditin (139 mg, 0.24 mmol, 1.2 eq.) were added in one portion to degassed tetrahydrofuran (10 mL) at room temperature. The reaction mixture was heated to 60 °C and stirred for 48 hours. The solvent was removed under reduced pressure and the remaining liquid was subjected to column chromatography. Elution with 10% ethyl acetate/light petroleum afforded the stannane **207** as a colourless oil (44 mg, 42%).

^1H NMR (400 MHz, CDCl_3): δ 7.98 (1 H, d, $J = 7.6$ Hz), 7.69 (1 H, d, $J = 7.2$ Hz), 7.48 (1 H, dd, $J = 7.2, 7.6$ Hz), 7.35 (1 H, dd, $J = 7.2, 7.6$ Hz), 5.01 (1 H, sp, $J = 6.2$ Hz), 3.07 (2 H, t, $J = 7.2$ Hz), 2.38 (2 H, t, $J = 7.2$ Hz), 2.04 (2 H, tt, $J = 7.2$ Hz), 1.49 (5 H, m), 1.27 (8 H, m), 1.22 (6 H, d, $J = 6.2$ Hz), 1.01 (5 H, m), 0.84 (9 H, t, J

= 7.2 Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 201.2 (C), 172.9 (C), 146.2 (C), 141.6 (C), 137.7 (CH), 132.1 (CH), 129.6 (CH), 128.2 (CH), 67.8 (CH), 37.4 (CH_2), 33.9 (CH_2), 29.4 (CH_2), 27.6 (CH_2), 22.0 (CH_3), 20.1 (CH_2), 13.9 (CH_3), 11.2 (CH_2) ppm; **ATR-FTIR**: 1731 (ester: $\text{C}=\text{O}$) and 1675 (ketone: $\text{C}=\text{O}$) cm^{-1} ; **HRMS (ASAP)**: $[\text{M}-57 (\text{C}_4\text{H}_9)]^+ \text{C}_{26}\text{H}_{44}\text{O}_3\text{Sn}$ requires 525.2391; found: 525.2407.

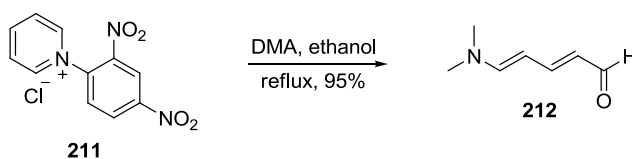
9.4.11 Preparation of the Zincke salt **211**



Following the procedure by Michels et al.,²⁵¹ a mixture of pyridine (1.38 g, 17.48 mmol, 1.0 eq.), 2,4-dinitro-1-chlorobenzene (3.54 g, 17.48 mmol, 1.0 eq.) and acetone (17 mL) was heated under reflux for 24 hours. The reaction mixture was cooled, filtered and the resulting precipitate was washed with light petroleum (3 x 5 mL) to give compound **211** as a white solid (4.58 g, 93%). The ^1H NMR spectrum matched the spectrum reported by Michels et al.²⁵¹

^1H NMR (400 MHz, DMSO): δ 9.38 (2 H, br. s), 9.12 (1 H, s), 8.97 (1 H, d, J = 8.7 Hz), 8.93 (1 H, t, J = 7.9 Hz), 8.43 (3 H, m) ppm.

9.4.12 Preparation of the Zincke aldehyde **212**

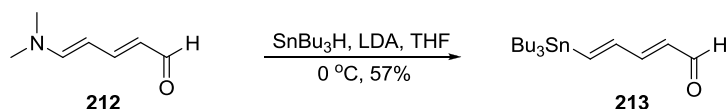


Following the procedure by Michels et al.,²⁵¹ dimethylamine (25% w/v in water, 5.76 g, 31.95 mmol, 2.5 eq.) was added dropwise to compound **211** (3.6 g, 12.78 mmol, 1.0 eq.) in ethanol (60 mL) at room temperature. The reaction mixture was heated under reflux for 1 hour. The mixture was cooled to 0 °C and NaOH (4 M, 50 mL) was added in small portions. The mixture was diluted with chloroform (100 mL) and washed with deionised water (2 x 20 mL). The organic layer was dried and the solvent removed under reduced pressure to give a black solid. The solid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 100% ethyl acetate afforded the aldehyde **212** as a

brown solid (1.52 g, 95%). The ^1H NMR spectrum matched the spectrum reported by Michels et al.²⁵¹

^1H NMR (400 MHz, CDCl_3): δ 9.24 (1 H, d, $J = 8.4$ Hz), 7.09 (1 H, dd, $J = 11.6, 14.3$ Hz), 6.77 (1 H, d, $J = 12.6$ Hz), 5.83 (1 H, dd, $J = 8.4, 14.3$ Hz), 5.26 (1 H, t, $J = 12.6$ Hz), 2.94 (6 H, s) ppm.

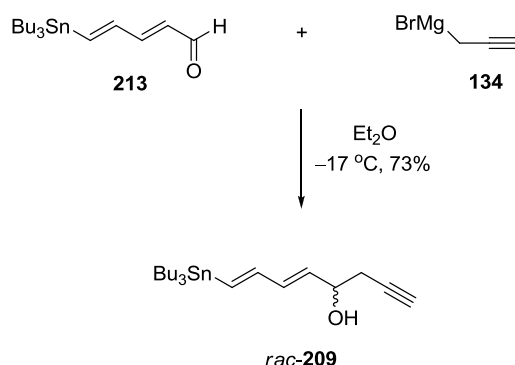
9.4.13 Synthesis of the stannane **213**



Following the procedure by Michels et al.,²⁵¹ *n*-BuLi (1.6 M in hexanes, 10.41 mL, 16.67 mmol, 1.5 eq.) was added dropwise to a solution of anhydrous diisopropylamine (1.46 g, 14.44 mmol, 1.3 eq.) in anhydrous tetrahydrofuran (20 mL) at 0 °C and the reaction mixture was stirred for 20 minutes. Tributyltin hydride (3.56 g, 12.22 mmol, 1.1 eq.) was then added dropwise and the mixture was stirred at 0 °C for a further 20 minutes. Compound **212** (1.39 g, 11.11 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (5 mL) was added dropwise at 0 °C and the reaction mixture was allowed to gradually warm to room temperature over 10 minutes. The reaction was quenched with acetyl chloride (3 mL) and the mixture was stirred for 10 minutes at room temperature. A saturated aqueous solution of NaHCO_3 (30 mL) was added dropwise and the reaction mixture was stirred for a further 10 minutes. The mixture was diluted with dichloromethane (20 mL) and washed with deionised water (2 x 10 mL). The organic layer was dried and the solvent removed under reduced pressure to give a black liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 10% ethyl acetate/light petroleum afforded the stannane **213** as a red oil (2.35 g, 57%). The ^1H NMR spectrum matched the spectrum reported by Michels et al.²⁵¹

^1H NMR (400 MHz, CDCl_3): δ 9.55 (1 H, d, $J = 8.0$ Hz), 7.03 (1 H, d, $J = 18.8$ Hz), 6.99 (1 H, dd, $J = 10.1, 15.2$ Hz), 6.79 (1 H, dd, $J = 10.1, 18.8$ Hz), 6.05 (1 H, dd, $J = 8.0, 15.2$ Hz), 1.48–1.53 (5 H, m), 1.25–1.37 (7 H, m), 0.96 (5 H, t, $J = 8.2$ Hz), 0.89 (10 H, t, $J = 7.3$ Hz) ppm.

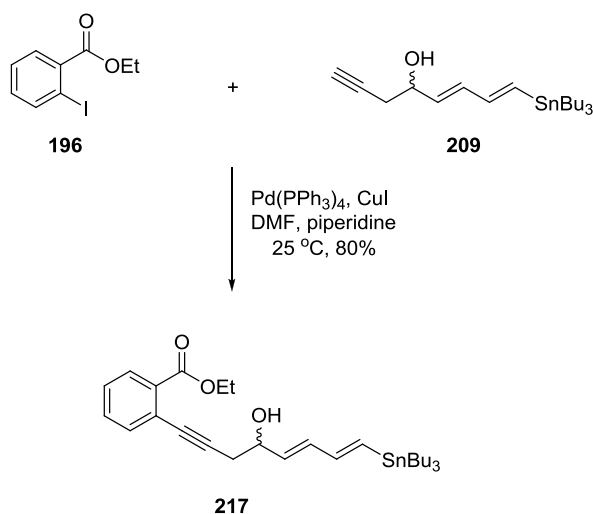
9.4.14 Propargylation of compound **213**



Propargyl bromide (80% w/v in toluene, 485 mg, 3.26 mmol, 1.1 eq.) was added in one portion to a mixture of magnesium turnings (144 mg, 5.93 mmol, 2.0 eq.), iodine (4 mg, 0.03 mmol) and HgCl_2 (9 mg, 0.03 mmol) in anhydrous ether (1 mL) at 0 °C. The reaction mixture was stirred for 20 minutes at 0 °C then cooled to −17 °C. Compound **213** (1.10 g, 2.96 mmol, 1.0 eq.) in anhydrous ether (2 mL) was added dropwise and the mixture was stirred for two and a half hours. A saturated aqueous solution of NH_4Cl (3 mL) was then added dropwise at 0 °C. The mixture was diluted with ether (15 mL) and washed with deionised water (2 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 20% ethyl acetate/light petroleum afforded *rac*-**209** as a colourless liquid (890 mg, 73%).

^1H NMR (400 MHz, CDCl_3): δ 6.52 (1 H, dd, J = 9.6, 18.9 Hz), 6.29 (1 H, d, J = 18.9 Hz), 6.26 (1 H, dd, J = 9.6, 16.3 Hz), 5.70 (1 H, dd, J = 6.5, 16.3 Hz), 4.34 (1 H, m), 2.47 (2 H, ddd, J = 2.6, 5.4, 16.7 Hz), 2.06 (1 H, t, J = 2.6 Hz), 2.05 (1 H, br. s), 1.47–1.52 (6 H, m), 1.25–1.31 (6 H, m), 0.89 (6 H, m), 0.88 (9 H, t, J = 7.3 Hz) ppm; **^{13}C NMR** (100 MHz, CDCl_3): δ 145.8 (CH), 136.2 (CH), 134.7 (CH), 132.3 (CH), 80.5 (CH), 71.1 (C), 70.5 (CH), 29.2 (CH_2), 27.8 (CH_2), 27.4 (CH_2), 13.8 (CH_3), 9.6 (CH_2) ppm; **ATR-FTIR**: 3333 (OH) cm^{-1} ; **HRMS (ASAP)**: $[\text{M}-18 (\text{H}_2\text{O})]^+ \text{C}_{20}\text{H}_{36}\text{OSn}$ requires 395.1761; found: 395.1761.

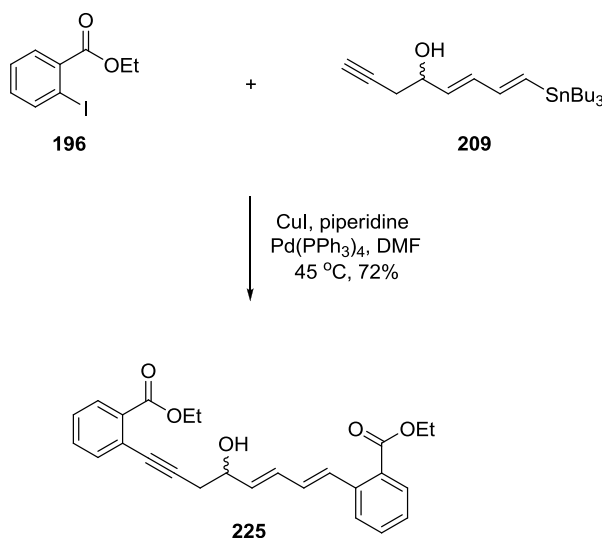
9.4.15

Sonogashira reaction between the iodide **196** and compound **209**

Compound **209** (50 mg, 0.12 mmol, 1.0 eq.), $\text{Pd(PPh}_3)_4$ (10 mg, 0.01 mmol, 7 mol%), CuI (2 mg, 0.01 mmol, 10 mol%), piperidine (21 mg, 0.24 mmol, 2.0 eq.) and BHT (1 crystal) were added in one portion to the iodide **196** (34 mg, 0.12 mmol, 1.0 eq.) in degassed anhydrous dimethylformamide (1 mL) and the mixture was stirred for 4 hours at room temperature. The reaction mixture was diluted with ether (10 mL) and washed with deionised water (3 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 20% ethyl acetate/light petroleum afforded compound **217** as a colourless oil (54 mg, 80%).

^1H NMR (400 MHz, CDCl_3): δ 7.97 (1 H, d, $J = 7.9$ Hz), 7.51 (1 H, d, $J = 7.3$ Hz), 7.48 (1 H, dd, $J = 7.3, 7.9$ Hz), 7.34 (1 H, dd, $J = 7.3, 7.3$ Hz), 6.53 (1 H, dd, $J = 9.8, 18.7$ Hz), 6.32 (1 H, dd, $J = 9.8, 15.3$ Hz), 6.26 (1 H, d, $J = 18.7$ Hz), 5.78 (1 H, dd, $J = 6.1, 15.3$ Hz), 4.46 (1 H, m), 4.39 (2 H, q, $J = 7.1$ Hz), 3.84 (1 H, d, $J = 5.1$ Hz), 2.78 (1 H, dd, $J = 4.1, 16.9$ Hz), 2.65 (1 H, dd, $J = 4.1, 16.9$ Hz), 1.47–1.51 (6 H, m), 1.38 (3 H, t, $J = 7.1$ Hz), 1.26–1.32 (6 H, m), 0.83–0.94 (15 H, m) ppm; **^{13}C NMR** (100 MHz, CDCl_3): δ 166.2 (C), 146.2 (CH), 135.1 (CH), 134.2 (CH), 133.7 (CH), 132.9 (CH), 132.0 (CH), 131.9 (C), 130.5 (CH), 127.6 (CH), 124.4 (C), 92.4 (C), 82.6 (C), 70.6 (CH), 61.5 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 27.4 (CH_2), 14.4 (CH_3), 13.8 (CH_3), 9.6 (CH_2) ppm; **ATR-FTIR**: 3506 (OH) and 1715 (C=O) cm^{-1} ; **HRMS (ASAP)**: $[\text{M}-18 (\text{H}_2\text{O})]^+ \text{C}_{29}\text{H}_{44}\text{O}_3\text{Sn}$ requires 543.2285; found: 543.2296.

9.4.16 Synthesis of compound **225**

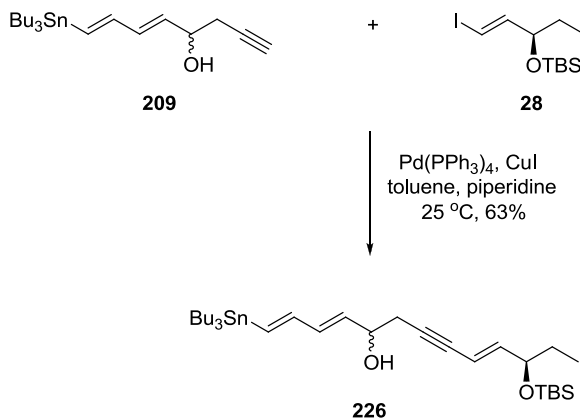


Compound **209** (69 mg, 0.17 mmol, 1.0 eq.), Pd(PPh₃)₄ (14 mg, 0.01 mmol, 7 mol%), CuI (3 mg, 0.02 mmol, 10 mol%), piperidine (29 mg, 0.34 mmol, 2.0 eq.) and BHT (1 crystal) were added in one portion to the iodide **196** (93 mg, 0.34 mmol, 2.0 eq.) in degassed anhydrous dimethylformamide (1 mL) at room temperature. The mixture was heated for 12 hours at 45 °C. The reaction mixture was diluted with ether (10 mL) and washed with deionised water (3 x 10 mL). The organic layer was dried and the solvent removed under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 40% ethyl acetate/light petroleum afforded compound **225** as a yellow oil (51 mg, 72%).

¹H NMR (400 MHz, CDCl₃): δ 8.00 (1 H, d, *J* = 7.8 Hz), 7.88 (1 H, d, *J* = 7.8 Hz), 7.62 (1 H, d, *J* = 7.8 Hz), 7.55 (1 H, d, *J* = 7.8 Hz), 7.48 (2 H, m), 7.41 (1 H, d, *J* = 15.4 Hz), 7.36 (1 H, dd, *J* = 7.8, 7.8 Hz), 7.30 (1 H, dd, *J* = 7.8, 7.8 Hz), 6.73 (1 H, dd, *J* = 10.6, 15.4 Hz), 6.60 (1 H, dd, *J* = 10.6, 15.2 Hz), 6.01 (1 H, dd, *J* = 6.1, 15.2 Hz), 4.57 (1 H, m), 4.41 (4 H, q, *J* = 7.1 Hz), 3.95 (1 H, d, *J* = 4.3 Hz), 2.83 (1 H, dd, *J* = 4.2, 16.9 Hz), 2.70 (1 H, dd, *J* = 4.2, 16.9 Hz), 1.41 (6 H, t, *J* = 7.1 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 167.4 (C), 166.2 (C), 138.7 (C), 135.5 (CH), 133.8 (CH), 132.0 (C), 131.9 (CH), 131.9 (CH), 131.4 (CH), 131.4 (CH), 131.1 (CH), 130.6 (CH), 130.6 (CH), 129.1 (C), 127.7 (CH), 127.2 (CH), 126.8 (CH), 124.4 (C), 92.2 (C), 82.7 (C), 70.7 (CH), 61.5 (CH₂), 61.2 (CH₂), 29.7 (CH₂), 14.5

(CH₃), 14.4 (CH₃) ppm; **ATR-FTIR**: 3496 (OH) and 1713 (2 x C=O) cm⁻¹; **HRMS (ESI)**: [M+23 (Na)]⁺ C₂₆H₂₆O₅ requires 441.1678; found: 441.1686.

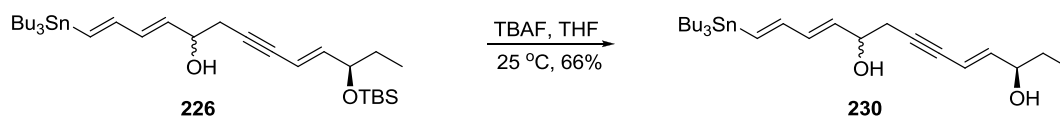
9.4.17 Sonogashira reaction between compound **209** and the iodide **28**



The iodide **28** (66 mg, 0.20 mmol, 1.2 eq.), Pd(PPh₃)₄ (14 mg, 0.01 mmol, 7 mol%), CuI (3 mg, 0.02 mmol, 10 mol%), piperidine (34 μL, 0.34 mmol, 2.0 eq.) and BHT (1 crystal) were added in one portion to compound **209** (69 mg, 0.17 mmol, 1.0 eq.) in degassed anhydrous toluene (1 mL) and the mixture was stirred for 2 hours at room temperature. The mixture was diluted with ether (10 mL) and washed with deionised water (3 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 5% ethyl acetate/light petroleum afforded the stannane **226** as a colourless oil (64 mg, 63%).

¹H NMR (400 MHz, CDCl₃): δ 6.52 (1 H, dd, *J* = 10.0, 18.7 Hz), 6.29 (1 H, d, *J* = 18.7 Hz), 6.22 (1 H, dd, *J* = 10.0, 16.0 Hz), 6.07 (1 H, dd, *J* = 5.4, 16.0 Hz), 5.72 (1 H, dd, *J* = 6.5, 15.8 Hz), 5.64 (1 H, dd, *J* = 1.6, 15.8 Hz), 4.33 (1 H, m), 4.09 (1 H, m), 2.60 (1 H, ddd, *J* = 1.6, 4.7, 16.8 Hz), 2.56 (1 H, ddd, *J* = 1.6, 4.7, 16.8 Hz), 2.01 (1 H, d, *J* = 4.6 Hz), 1.47–1.52 (8 H, m), 1.25–1.36 (6 H, m), 0.90 (9 H, s), 0.89 (18 H, m), 0.05 (3 H, s), 0.03 (3 H, s) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 146.2 (CH), 145.9 (CH), 135.9 (CH), 134.6 (CH), 132.6 (CH), 108.7 (CH), 85.7 (C), 81.7 (C), 73.7 (CH), 70.7 (CH), 30.8 (CH₂), 29.2 (CH₂), 28.9 (CH₂), 27.4 (CH₂), 26.0 (CH₃), 18.4 (C), 13.8 (CH₃), 9.7 (CH₂), 9.4 (CH₃), -4.4 (CH₃), -4.7 (CH₃) ppm; **ATR-FTIR**: 3381 (OH) cm⁻¹; **HRMS (ASAP)**: [M-18 (H₂O)]⁺ C₃₁H₅₈O₂SiSn requires 593.3201; found: 593.3218.

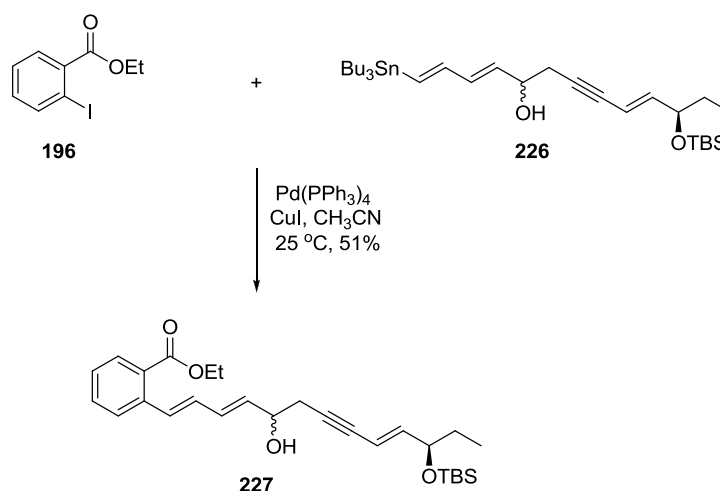
9.4.18 Treatment of the stannane **226** with TBAF



TBAF (1 M in tetrahydrofuran, 0.90 mL, 3.44 mmol, 5.0 eq.) was added dropwise to the stannane **226** (420 mg, 0.69 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (5 mL) at $-84\text{ }^\circ\text{C}$. The reaction mixture was allowed to warm to room temperature and stirred for 12 hours. The mixture was concentrated under reduced pressure and the remaining liquid was subjected to column chromatography. The column was conditioned with triethylamine (1%). Elution with 40% ethyl acetate/light petroleum afforded the stannane **230** as a colourless oil (225 mg, 66%).

^1H NMR (400 MHz, CDCl_3): 6.52 (1 H, dd, $J = 9.9, 18.7$ Hz), 6.29 (1 H, d, $J = 18.7$ Hz), 6.28 (1 H, dd, $J = 9.9, 16.2$ Hz), 6.10 (1 H, dd, $J = 6.2, 16.2$ Hz), 5.70 (2 H, m), 4.33 (1 H, m), 4.08 (1 H, m), 2.63 (1 H, ddd, $J = 1.6, 5.3, 16.8$ Hz), 2.56 (1 H, ddd, $J = 1.6, 5.3, 16.8$ Hz), 1.98 (1 H, d, $J = 4.6$ Hz), 1.48–1.53 (7 H, m), 1.25–1.36 (7 H, m), 0.81–0.97 (18 H, m) ppm; **^{13}C NMR** (100 MHz, CDCl_3): δ 145.9 (CH), 145.2 (CH), 136.1 (CH), 134.6 (CH), 132.5 (CH), 110.2 (CH), 86.5 (C), 81.2 (C), 73.8 (CH), 70.7 (CH), 30.0 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 27.4 (CH_2), 13.8 (CH_3), 9.7 (CH_2), 9.7 (CH_3) ppm; **ATR-FTIR**: 3381 (2 x OH) cm^{-1} ; **HRMS (ESI)**: Molecular ion not found.

9.4.19 Stille reaction between the iodide **196** and the stannane **226**

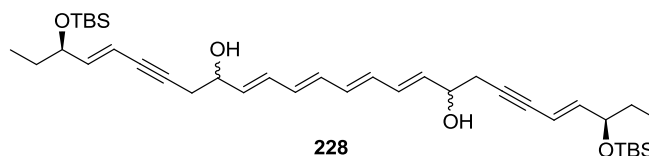


The iodide **196** (9 mg, 0.03 mmol, 1.0 eq.), $\text{Pd}(\text{PPh}_3)_4$ (3 mg, 2.26 μmol , 7 mol%), CuI (1 mg, 3.23 μmol , 10 mol%) and BHT (1 crystal) were added in one portion to compound **226** (16 mg, 0.03 mmol, 1.0 eq.) in degassed anhydrous acetonitrile (1 mL) and the mixture was stirred for 12 hours at room temperature. After this time, another portion of $\text{Pd}(\text{PPh}_3)_4$ (3 mg, 2.26 μmol , 7 mol%) was added and the reaction mixture was stirred for an additional 60 hours. The mixture was diluted with ether (5 mL) and washed with deionised water (3 x 10 mL). The organic layer was dried and the solvent removed under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 20% ethyl acetate/light petroleum afforded compound **227** as a colourless oil (8 mg, 51%).

^1H NMR (400 MHz, CDCl_3): δ 7.87 (1 H, d, $J = 7.9$ Hz), 7.60 (1 H, d, $J = 7.9$ Hz), 7.46 (1 H, dd, $J = 7.9, 7.9$ Hz), 7.41 (1 H, d, $J = 15.4$ Hz), 7.29 (1 H, dd, $J = 7.9, 7.9$ Hz), 6.70 (1 H, dd, $J = 10.4, 15.4$ Hz), 6.53 (1 H, dd, $J = 10.4, 15.2$ Hz), 6.08 (1 H, dd, $J = 5.4, 15.8$ Hz), 5.92 (1 H, dd, $J = 6.3, 15.2$ Hz), 5.64 (1 H, dt, $J = 1.6, 15.8$ Hz), 4.40 (1 H, m), 4.37 (2 H, q, $J = 7.1$ Hz), 4.10 (1 H, m), 2.66 (1 H, ddd, $J = 1.6, 5.3, 16.8$ Hz), 2.59 (1 H, ddd, $J = 1.6, 5.3, 16.8$ Hz), 2.07 (1 H, d, $J = 4.6$ Hz), 1.51 (2 H, m), 1.40 (3 H, t, $J = 7.1$ Hz), 0.90 (9 H, s), 0.87 (3 H, t, $J = 7.5$ Hz), 0.04 (3 H, s), 0.03 (3 H, s) ppm; **^{13}C NMR** (100 MHz, CDCl_3): δ 167.6 (C), 146.2 (CH), 138.7 (C), 135.2 (CH), 132.0 (CH), 131.9 (CH), 131.9 (CH), 130.8 (CH), 130.6 (CH), 129.1 (C), 127.3 (CH), 126.9 (CH), 108.7 (CH), 85.5 (C), 81.8 (C), 73.7 (CH), 70.8 (CH), 61.2 (CH_2), 30.8 (CH_2), 29.0 (CH_2), 26.0 (CH_3), 18.4 (C), 14.5 (CH_3), 9.4

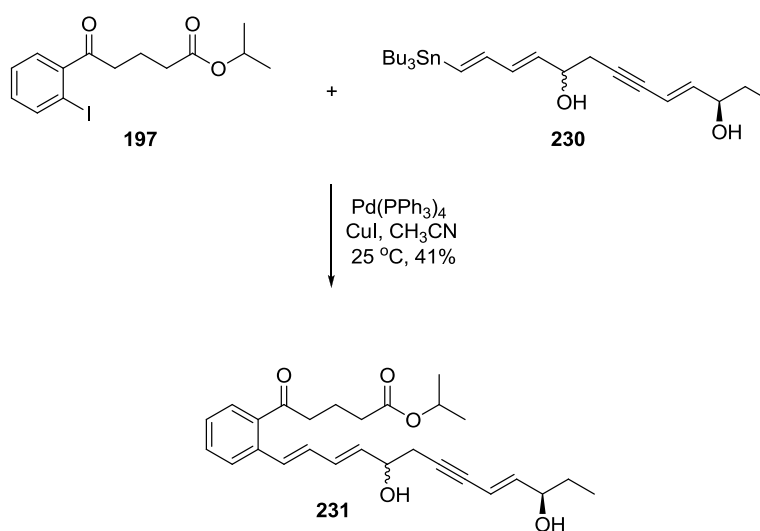
(CH₃), -4.4 (CH₃), -4.7 (CH₃) ppm; **ATR-FTIR**: 3450 (OH) and 1729 (C=O) cm⁻¹; **HRMS (ESI)**: [M⁺] C₂₈H₄₀O₄Si requires 469.2774; found: 469.2786.

The reaction was repeated in anhydrous dimethylformamide to afford the dimer **228** in 65% yield.



¹H NMR (400 MHz, CDCl₃): δ 6.35 (2 H, dd, *J* = 9.1, 14.8 Hz), 6.27 (4 H, br. s), 6.06 (2 H, dd, *J* = 5.4, 15.8 Hz), 5.79 (2 H, dd, *J* = 6.3, 14.8 Hz), 5.63 (2 H, dt, *J* = 1.6, 15.8 Hz), 4.35 (2 H, m), 4.09 (2 H, m), 2.63 (2 H, ddd, *J* = 1.6, 5.1, 16.5 Hz), 2.56 (2 H, ddd, *J* = 1.6, 5.1, 16.5 Hz), 2.03 (2 H, d, *J* = 4.9 Hz), 1.48–1.52 (4 H, m), 0.90 (18 H, s), 0.87 (6 H, t, *J* = 7.5 Hz), 0.05 (6 H, s), 0.03 (6 H, s) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 146.2 (CH), 134.4 (CH), 133.5 (CH), 132.5 (CH), 131.5 (CH), 108.7 (CH), 85.5 (C), 81.8 (C), 73.7 (CH), 70.8 (CH), 30.8 (CH₂), 29.0 (CH₂), 26.0 (CH₃), 18.4 (C), 9.4 (CH₃), -4.4 (CH₃), -4.7 (CH₃) ppm; **HRMS (ESI)**: Molecular ion not found.

9.4.20 Stille reaction between the iodide **197** and the stannane **230**

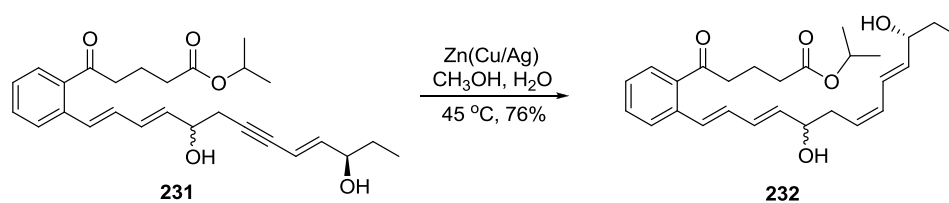


The iodide **197** (43 mg, 0.12 mmol, 1.3 eq.), Pd(PPh₃)₄ (8 mg, 6.50 μmol, 7 mol%), CuI (2 mg, 9.29 μmol, 10 mol%) and BHT (1 crystal) were added to compound **230** (46 mg, 0.09 mmol, 1.0 eq.) in degassed acetonitrile (1 mL) and the mixture was stirred for 12 hours at room temperature. The mixture was diluted with ether (5 mL)

and washed with deionised water (3 x 10 mL). The organic layer was dried and the solvent removed under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 50% ethyl acetate/light petroleum afforded compound **231** as a light brown oil (17 mg, 41%, 92% brsm).

¹H NMR (400 MHz, CDCl₃): δ 7.58 (2 H, d, *J* = 7.4 Hz), 7.43 (1 H, dd, *J* = 7.4, 7.4 Hz), 7.30 (1 H, dd, *J* = 7.4, 7.4 Hz), 7.01 (1 H, d, *J* = 15.8 Hz), 6.66 (1 H, dd, *J* = 10.5, 15.8 Hz), 6.50 (1 H, dd, *J* = 10.5, 15.5 Hz), 6.08 (1 H, dd, *J* = 6.3, 15.9 Hz), 5.91 (1 H, dd, *J* = 6.3, 15.5 Hz), 5.64 (1 H, dt, *J* = 1.4, 15.9 Hz), 5.01 (1 H, sp, *J* = 6.3 Hz), 4.39 (1 H, m), 4.09 (1 H, m), 2.95 (2 H, t, *J* = 7.2 Hz), 2.67 (1 H, ddd, *J* = 1.4, 5.3, 16.8 Hz), 2.58 (1 H, ddd, *J* = 1.4, 5.3, 16.8 Hz), 2.37 (2 H, t, *J* = 7.2 Hz), 2.06 (1 H, d, *J* = 3.2 Hz), 2.03 (2 H, tt, *J* = 7.2, 7.2 Hz), 1.67 (1 H, d, *J* = 4.1 Hz), 1.62 (2 H, m), 1.25 (6 H, d, *J* = 6.3 Hz), 0.96 (3 H, t, *J* = 7.5 Hz) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 204.3 (C), 172.9 (C), 145.3 (CH), 137.7 (C), 136.7 (C), 135.2 (CH), 131.8 (CH), 131.6 (CH), 131.4 (CH), 131.0 (CH), 128.4 (CH), 127.4 (CH), 127.3 (CH), 110.1 (CH), 86.3 (C), 81.3 (C), 73.8 (CH), 70.8 (CH), 67.9 (CH), 41.0 (CH₂), 33.9 (CH₂), 30.0 (CH₂), 28.8 (CH₂), 22.0 (CH₃), 19.8 (CH₂), 9.7 (CH₃) ppm; **HRMS (ESI)**: [M+23 (Na)]⁺ C₂₇H₃₄O₅ requires 461.2304; found: 461.2316.

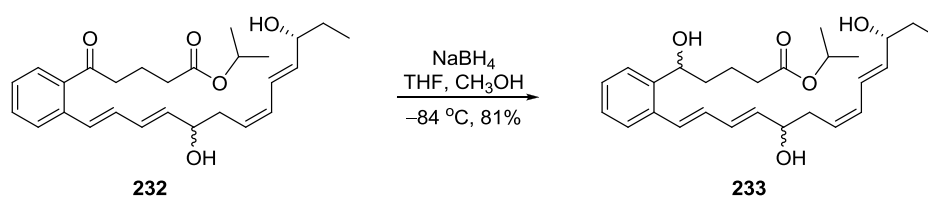
9.4.21 Reduction of the alkyne **231**



A Zn(Cu/Ag) amalgam²⁶⁵ (470 mg, 1.98 mmol, 108.8 eq.) was added in one portion to a nitrogen purged solution of the alkyne **231** (8 mg, 0.02 mol, 1.0 eq.) in methanol (1 mL) and deionised water (1 mL) at room temperature. The reaction mixture was heated at 45 °C for 21 hours. The mixture was filtered to remove the Zn(Cu/Ag) solid and the filtrate was concentrated under reduced pressure to give a brown liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 70% ethyl acetate/light petroleum afforded compound **232** as a colourless oil (6 mg, 76%).

¹H NMR (400 MHz, CDCl₃): δ 7.57 (2 H, d, *J* = 7.9 Hz), 7.43 (1 H, dd, *J* = 7.9, 7.9 Hz), 7.31 (1 H, dd, *J* = 7.9, 7.9 Hz), 7.00 (1 H, d, *J* = 15.4 Hz), 6.65 (1 H, dd, *J* = 10.6, 15.4 Hz), 6.51 (1 H, dd, *J* = 10.9, 15.2 Hz), 6.45 (1 H, dd, *J* = 10.6, 15.3 Hz), 6.17 (1 H, t, *J* = 10.9 Hz), 5.87 (1 H, dd, *J* = 6.5, 15.3 Hz), 5.73 (1 H, dd, *J* = 6.6, 15.2 Hz), 5.50 (1 H, dt, *J* = 7.6, 10.9 Hz), 5.10 (1 H, sp, *J* = 6.3 Hz), 4.30 (1 H, m), 4.11 (1 H, m), 2.95 (2 H, t, *J* = 7.2 Hz), 2.51 (2 H, m), 2.37 (2 H, t, *J* = 7.2 Hz), 2.03 (2 H, tt, *J* = 7.2, 7.2 Hz), 1.68 (2 H, br. s), 1.60 (2 H, m), 1.23 (6 H, d, *J* = 6.3 Hz), 0.93 (3 H, t, *J* = 7.4 Hz) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 204.3 (C), 172.8 (C), 137.8 (C), 137.3 (CH), 136.8 (C), 136.6 (CH), 131.4 (CH), 131.2 (CH), 131.2 (CH), 131.1 (CH), 131.1 (CH), 128.3 (CH), 127.4 (CH), 127.2 (CH), 126.9 (CH), 125.7 (CH), 74.2 (CH), 72.1 (CH), 67.9 (CH), 41.1 (CH₂), 35.8 (CH₂), 33.9 (CH₂), 30.3 (CH₂), 22.0 (CH₃), 19.8 (CH₂), 9.9 (CH₃) ppm; **HRMS (ESI)**: [M+23 (Na)]⁺ C₂₇H₃₆O₅ requires 463.2460; found: 463.2461.

9.4.22 Reduction of the ketone **232**

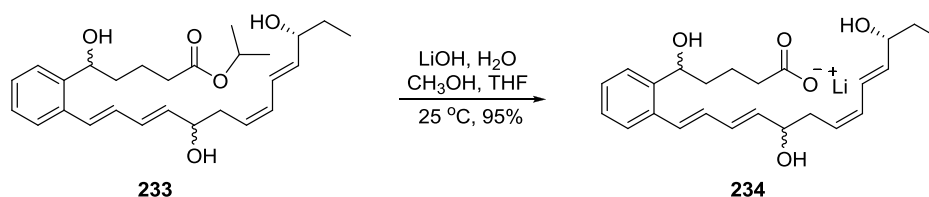


NaBH₄ (26 mg, 0.68 mmol, 2.5 eq.) was added in small portions to the ketone **232** (120 mg, 0.27 mmol, 1.0 eq.) in tetrahydrofuran (3 mL) and methanol (3 mL) at -84 °C and the reaction mixture was stirred for 3 hours. The reaction was quenched with a saturated aqueous solution of NH₄Cl (2 mL) and the mixture was stirred for a further 30 minutes. The mixture was diluted with ethyl acetate (10 mL) and washed with deionised water (2 x 2 mL). The organic layer was dried and the solvent removed under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 50% ethyl acetate/light petroleum afforded compound **233** as a colourless oil (98 mg, 81%).

¹H NMR (400 MHz, CDCl₃): δ 7.48 (2 H, m), 7.26 (2 H, m), 6.89 (1 H, d, *J* = 15.3 Hz), 6.64 (1 H, dd, *J* = 10.5, 15.3 Hz), 6.47 (2 H, m), 6.18 (1 H, t, *J* = 10.9 Hz), 5.86 (1 H, dd, *J* = 6.6, 15.2 Hz), 5.74 (1 H, dd, *J* = 6.7, 15.2 Hz), 5.04 (1 H, dt, *J* = 7.8, 10.9 Hz), 5.00 (2 H, m), 4.31 (1 H, m), 4.11 (1 H, m), 2.52 (2 H, m), 2.31 (2 H,

t, $J = 7.1$ Hz), 1.69–1.81 (7 H, m), 1.59 (2 H, m), 1.17 (6 H, d, $J = 6.3$ Hz), 0.93 (3 H, t, $J = 7.4$ Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 173.3 (C), 141.8 (C), 137.3 (CH), 136.0 (CH), 134.9 (C), 131.2 (CH), 130.7 (CH), 129.6 (CH), 128.0 (CH), 127.7 (CH), 126.9 (CH), 126.1 (CH), 125.8 (CH), 125.8 (CH), 125.6 (CH), 74.1 (CH), 72.1 (CH), 70.6 (CH), 67.8 (CH), 37.8 (CH_2), 35.9 (CH_2), 34.5 (CH_2), 30.3 (CH_2), 22.0 (CH_3), 21.6 (CH_2), 9.9 (CH_3) ppm; **LRMS (ESI)**: m/z 465 (M^+ , 100%), 407 (9), 235 (4), 150 (18), 102 (96); **HRMS (ESI)**: Molecular ion not found.

9.4.23 Synthesis of benzoeresolvin E1 **234**

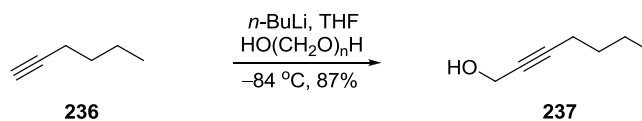


LiOH (2 mg, 0.07 mmol, 3.0 eq.) was added in one portion to a solution of compound **233** (10 mg, 0.02 mmol, 1.0 eq.) in tetrahydrofuran (0.5 mL), methanol (0.2 mL) and deionised water (0.2 mL) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to afford the target compound **234** as a light brown oil (9 mg, 95%).

^1H NMR (400 MHz, CD_3OD): δ 7.47 (2 H, m), 7.72 (1 H, m), 7.19 (1 H, m), 6.94 (1 H, d, $J = 15.6$ Hz), 6.67 (1 H, dd, $J = 10.5, 15.6$ Hz), 6.53 (1 H, dd, $J = 11.0, 15.2$ Hz), 6.45 (1 H, dd, $J = 10.5, 15.4$ Hz), 6.10 (1 H, t, $J = 11.0$ Hz), 5.84 (1 H, dd, $J = 6.2, 15.4$ Hz), 5.66 (1 H, dd, $J = 6.7, 15.2$ Hz), 5.49 (1 H, dt, $J = 7.9, 11.0$ Hz), 4.99 (1 H, m), 4.21 (1 H, m), 4.02 (1 H, m), 2.48 (2 H, m), 2.18 (2 H, t, $J = 7.9$ Hz), 1.71–1.76 (3 H, m), 1.63 (1 H, m), 1.48–1.56 (2 H, m), 0.91 (3 H, t, $J = 7.5$ Hz) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 182.7 (C), 143.7 (C), 137.8 (CH), 137.4 (CH), 136.1 (C), 132.1 (CH), 131.6 (CH), 131.1 (CH), 130.6 (CH), 128.5 (CH), 128.1 (CH), 128.1 (CH), 127.0 (CH), 126.7 (CH), 126.6 (CH), 74.7 (CH), 73.1 (CH), 71.1 (CH), 39.8 (CH_2), 38.9 (CH_2), 36.8 (CH_2), 31.2 (CH_2), 24.2 (CH_2), 10.2 (CH_3) ppm; **ATR-FTIR**: 3411 (3 x OH) and 1655 ($\text{C}=\text{O}$) cm^{-1} ; **HRMS (ESI)**: [M^+] $\text{C}_{24}\text{H}_{31}\text{LiO}_5$ requires 407.2410; found: 407.2422; **UV spectrum**: λ_{max} ($\log \epsilon$) = 272 (4.59) nm in MeOH.

9.5 Chapter 5 experimental procedures

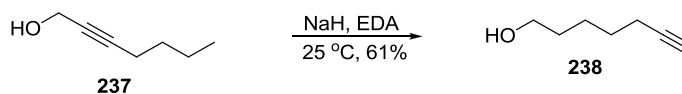
9.5.1 Preparation of hept-2-yn-1-ol



Following the procedure by Li and O'Doherty,³¹¹ $n\text{-BuLi}$ (1.6 M in hexanes, 61.0 mL, 0.10 mol, 1.0 eq.) was added dropwise to 1-hexyne (8.02 g, 0.10 mol, 1.0 eq.) in anhydrous tetrahydrofuran (100 mL) at $-84\text{ }^\circ\text{C}$. The solution was stirred for 1 hour at this temperature after which paraformaldehyde (2.93 g, 0.10 mol, 1.0 eq.) was added in small portions. The reaction mixture was allowed to warm to room temperature and stirred for 12 hours. The reaction was quenched with deionised water (15 mL) and the mixture was stirred for 30 minutes. The mixture was diluted with ether (100 mL) and washed with deionised water (2 x 20 mL). The organic layer was dried and concentrated under reduced pressure to give a yellow oil. The oil was subjected to column chromatography. Elution with 20% ethyl acetate/light petroleum afforded hept-2-yn-1-ol as a yellow oil (9.53 g, 87%). The ^1H NMR spectrum matched the spectroscopic data reported in the literature.³¹¹

^1H NMR (400 MHz, CDCl_3): δ 4.22 (2 H, m), 2.19 (2 H, m), 2.04 (1 H, br. s), 1.47 (2 H, m), 1.39 (2 H, m), 0.89 (3 H, t, $J = 7.3$ Hz) ppm.

9.5.2 Zipper reaction with hept-2-yn-1-ol

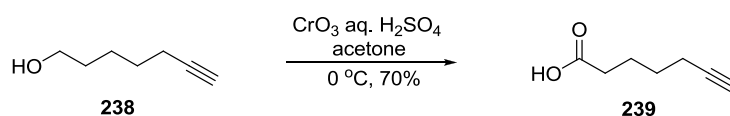


Adapting the procedure by Matovic et al.,²⁷¹ 60% NaH in mineral oil (16.08 g, 0.40 mol, 5.0 eq.) was added in small portions to anhydrous 1,2-ethylenediamine (100 mL) at $0\text{ }^\circ\text{C}$ over 15 minutes. The mixture was allowed to warm to room temperature and stirred for 2 hours. A solution of hept-2-yn-1-ol (9.02 g, 0.08 mol, 1.0 eq.) in anhydrous 1,2-ethylenediamine (2 mL) was added dropwise to the reaction mixture at room temperature and stirred for a further 4 hours. The reaction mixture was cooled to $0\text{ }^\circ\text{C}$ and quenched with 1 M HCl (30 mL). The mixture was diluted with ether (150 mL), washed with deionised water (2 x 30 mL), dried and concentrated under reduced pressure to afford a yellow liquid. The liquid was

subjected to column chromatography. Elution with 20% ethyl acetate/light petroleum gave the alcohol **238** as a yellow oil (5.50 g, 61%). The spectroscopic data matched that reported in the literature.²⁷¹

¹H NMR (400 MHz, CDCl₃): δ 3.52 (2 H, t, J = 6.5 Hz), 2.82 (1 H, s), 2.15 (2 H, ddd, J = 2.7, 7.1, 14.3 Hz), 1.88 (1 H, t, J = 2.7 Hz), 1.46–1.51 (4 H, m), 1.38 (2 H, m) ppm.

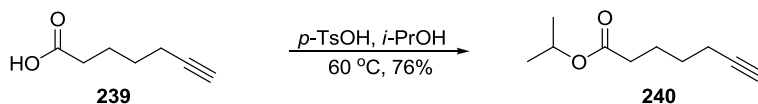
9.5.3 Oxidation of the alcohol **238** using Jones reagent



Jones reagent (1.3 M, 79.64 mL, 0.10 mol, 2.1 eq.) was added dropwise to the alcohol **238** (5.53 g, 0.05 mol, 1.0 eq.) in acetone (200 mL) and the mixture was stirred for 2 hours at 0 °C. Methanol (20 mL) was then added dropwise at this temperature, resulting in a suspension. The suspension was filtered and the filtrate was diluted with ethyl acetate (200 mL) and washed with deionised water (2 x 30 mL). The organic layer was dried and the solvent removed under reduced pressure to afford a brown liquid. The liquid was subjected to column chromatography. Elution with 30% ethyl acetate/light petroleum gave compound **239** as a colourless oil (4.35 g, 70%). The ¹H NMR spectrum matched that reported in the literature.³¹²

¹H NMR (400 MHz, CDCl₃): δ 2.39 (2 H, t, J = 7.3 Hz), 2.23 (2 H, ddd, J = 2.7, 6.8, 13.9 Hz), 1.96 (1 H, t, J = 2.7 Hz), 1.77 (2 H, m), 1.59 (2 H, m) ppm.

9.5.4 Esterification of compound **239**

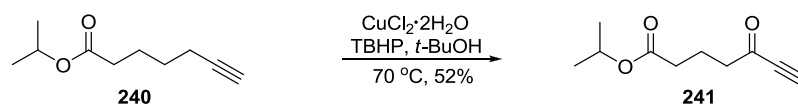


p-Toluenesulfonic acid (464 mg, 2.70 mmol, 0.1 eq.) was added in one portion to compound **239** (3.40 g, 26.95 mmol, 1.0 eq.) in anhydrous isopropyl alcohol (100 mL) at room temperature. The reaction mixture was heated at 60 °C for 16 hours. The mixture was diluted with ether (150 mL), washed with a saturated aqueous solution of Na₂CO₃ (20 mL) and washed with deionised water (2 x 10 mL).

The organic layer was dried and concentrated under reduced pressure to give the ester **240** as a colourless oil (3.45 g, 76%). The ^1H NMR spectrum matched that reported in the literature.³¹³

^1H NMR (400 MHz, CDCl_3): δ 5.00 (1 H, sp, $J = 6.3$ Hz), 2.28 (2 H, t, $J = 7.3$ Hz), 2.20 (2 H, ddd, $J = 2.7, 7.1, 14.1$ Hz), 1.94 (1 H, t, $J = 2.7$ Hz), 1.73 (2 H, m), 1.58 (2 H, m), 1.22 (6 H, d, $J = 6.3$ Hz) ppm.

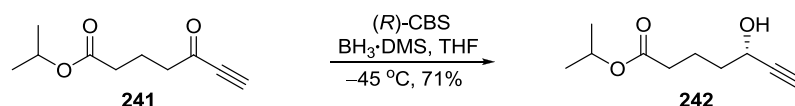
9.5.5 Propargylic oxidation of the ester **240**



Adapting the procedure by Li and co-workers,²⁷² $\text{CuCl}_2\cdot 2\text{H}_2\text{O}$ (125 mg, 0.73 mmol, 4 mol%) was added in one portion to the ester **240** (3.08 g, 18.31 mmol, 1.0 eq.) in *t*-butanol (75 mL). The reaction mixture was heated to 70 °C and *t*-butyl hydroperoxide (70% in water, 5.04 mL, 0.04 mol, 2.0 eq.) was added in four equal portions over 4 hours. After 24 hours, the reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The remaining residue was diluted with ether (50 mL), washed with deionised water (2 x 30 mL), dried and concentrated under reduced pressure to afford a yellow liquid. The liquid was subjected to column chromatography. Elution with 20% ethyl acetate/light petroleum gave the ketoester **241** as a colourless oil (1.73 g, 52%). The ^1H NMR spectrum matched that reported by Heiss and Phillips.²⁷³

^1H NMR (400 MHz, CDCl_3): δ 5.00 (1 H, sp, $J = 6.3$ Hz), 3.22 (1 H, s), 2.66 (2 H, t, $J = 7.3$ Hz), 2.31 (2 H, t, $J = 7.3$ Hz), 1.97 (2 H, tt, $J = 7.3, 7.3$ Hz), 1.22 (6 H, d, $J = 6.3$ Hz) ppm.

9.5.6 Asymmetric reduction of the ketoester **241**

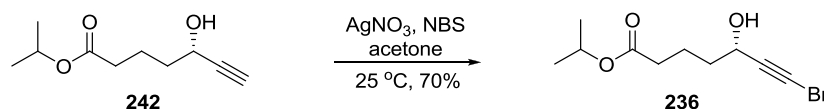


(*R*)-(+)-2-Methyl-CBS-oxazaborolidine (53 mg, 0.19 mmol, 7 mol%) was added to a solution of $\text{BH}_3\cdot\text{DMS}$ (21 mg, 26 μL , 0.27 mmol, 0.1 eq.) in anhydrous tetrahydrofuran (3 mL) and the mixture was stirred at room temperature for

15 minutes. The mixture was cooled to $-45\text{ }^{\circ}\text{C}$ and the ketoester **241** (500 mg, 2.74 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (3 mL) was added in one portion, followed by dropwise addition of $\text{BH}_3\cdot\text{DMS}$ (125 mg, 156 μL , 1.65 mmol, 0.6 eq.) over 2 hours. The reaction mixture was stirred for another 5 hours at this temperature. Methanol (4 mL) and a saturated aqueous solution of NH_4Cl (3 mL) were then added successively. The mixture was extracted with ethyl acetate (30 mL) and washed with deionised water (2 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 20% ethyl acetate/light petroleum afforded the alcohol **242** as a colourless oil (359 mg, 71%) in 91% *ee*. The ^1H NMR spectrum matched that reported by Heiss and Phillips.²⁷³

^1H NMR (400 MHz, CDCl_3): δ 5.00 (1 H, sp, $J = 6.3$ Hz), 4.38 (1 H, br. s), 2.46 (1 H, d, $J = 2.1$ Hz), 2.32 (2 H, t, $J = 6.6$ Hz), 2.10 (1 H, d, $J = 4.4$ Hz), 1.73–1.78 (4 H, m), 1.22 (6 H, d, $J = 6.3$ Hz) ppm; $[\alpha]_D^{23} = -9.40^{\circ}$ ($c = 1.00$, CHCl_3) as the (*S*)-alcohol, lit. $[\alpha]_D^{23} = +10.30^{\circ}$ ($c = 2.60$, CHCl_3) as the (*R*)-alcohol.²⁷³

9.5.7 Bromination of compound **242**

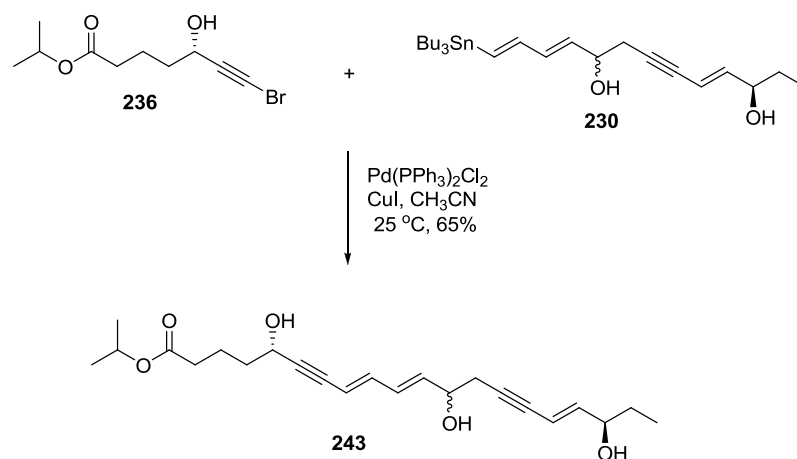


Silver nitrate (46 mg, 0.27 mmol, 0.2 eq.) was added in one portion to compound **242** (247 mg, 1.34 mmol, 1.0 eq.) in acetone (2 mL) and the mixture was stirred for 30 minutes at room temperature. *N*-bromosuccinimide (262 mg, 1.47 mmol, 1.1 eq.) was then added portionwise and the mixture was stirred for a further 12 hours at room temperature. The reaction mixture was filtered and the filtrate was diluted with ether (20 mL) and washed with deionised water (2 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give a brown oil. The oil was subjected to column chromatography. Elution with 20% ethyl acetate/light petroleum gave the bromide **236** as a light brown oil (247 mg, 70%).

^1H NMR (400 MHz, CDCl_3): δ 5.00 (1 H, sp, $J = 6.3$ Hz), 4.41 (1 H, t, $J = 6.2$ Hz), 2.84 (1 H, br. s), 2.32 (2 H, t, $J = 6.7$ Hz), 1.71–1.77 (4 H, m), 1.23 (6 H, d, $J =$

6.3 Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 173.1 (C), 80.9 (C), 67.9 (CH), 63.1 (CH), 45.5 (C), 37.0 (CH_2), 34.2 (CH_2), 22.0 (CH_3), 20.6 (CH_2) ppm; ATR-FTIR: 3447 (OH) and 1728 ($\text{C}=\text{O}$) cm^{-1} ; $[\alpha]_D^{24} = -9.27^\circ$ ($c = 1.00$, CHCl_3); HRMS (ESI): $[\text{M}+23(\text{Na})]^+$ $\text{C}_{10}\text{H}_{15}\text{BrO}_3$ requires 285.0102; found: 285.0108.

9.5.8 Stille reaction between the bromide **236** and the stannane **230**



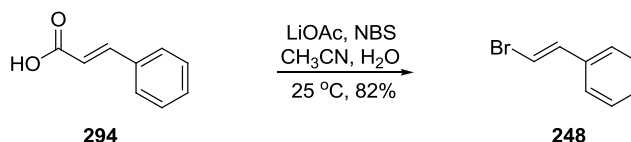
The bromide **236** (53 mg, 0.20 mmol, 1.0 eq.), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (10 mg, 0.01 mmol, 7 mol%), CuI (4 mg, 0.02 mmol, 10 mol%) and BHT (1 crystal) were added to the stannane **230** (100 mg, 0.20 mmol, 1.0 eq.) in degassed acetonitrile (2 mL) and the mixture was stirred for 13 hours at room temperature. The mixture was diluted with ethyl acetate (5 mL) and washed with deionised water (2 x 5 mL). The organic layer was dried and the solvent removed under reduced pressure to give an orange liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 70% ethyl acetate/light petroleum afforded compound **243** as a yellow oil (51 mg, 65%). The spectroscopic data matched that reported by Allard et al.¹⁸²

^1H NMR (400 MHz, CD_3OD): δ 6.58 (1 H, dd, $J = 10.8, 15.5$ Hz), 6.35 (1 H, dd, $J = 10.8, 15.3$ Hz), 6.00 (1 H, dd, $J = 6.2, 15.9$ Hz), 5.89 (1 H, dd, $J = 6.1, 15.2$ Hz), 5.67 (2 H, m), 5.00 (1 H, sp, $J = 6.3$ Hz), 4.45 (1 H, t, $J = 6.4$ Hz), 4.26 (1 H, q, $J = 6.2$ Hz), 3.97 (1 H, q, $J = 6.3$ Hz), 2.54 (1 H, ddd, $J = 2.1, 6.0, 16.7$ Hz), 2.50 (1 H, ddd, $J = 2.1, 6.0, 16.7$ Hz), 2.33 (2 H, t, $J = 7.3$ Hz), 1.75 (4 H, m), 1.51 (2 H, m), 1.23 (6 H, d, $J = 6.3$ Hz), 0.91 (3 H, t, $J = 7.4$ Hz) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 174.8 (C), 146.1 (CH), 142.3 (CH), 138.6 (CH), 130.9 (CH), 112.1 (CH), 110.9 (CH), 93.9 (C), 87.2 (C), 84.3 (C), 81.5 (C), 74.2 (CH), 71.5 (CH), 69.0 (CH),

62.9 (CH), 38.2 (CH₂), 35.1 (CH₂), 30.9 (CH₂), 29.0 (CH₂), 22.1 (CH₃), 22.0 (CH₂), 10.0 (CH₃) ppm.

9.6 Chapter 6 experimental procedures

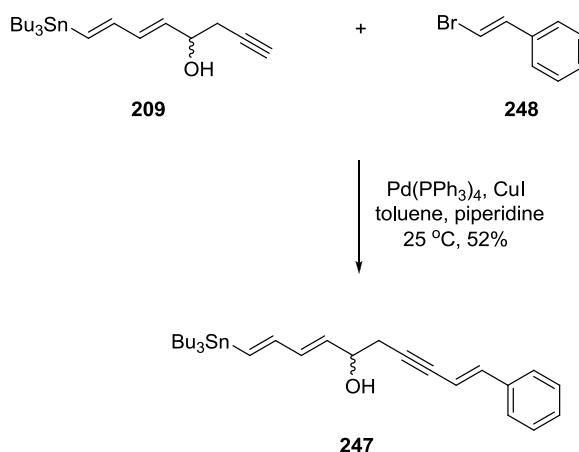
9.6.1 Vinylogous Hunsdiecker reaction with *trans*-cinnamic acid



Following the procedure by Kuang et al.,²⁷⁵ *trans*-cinnamic acid (2.45 g, 16.54 mmol, 1.0 eq.) was added in one portion to a mixture of lithium acetate (218 mg, 3.31 mmol, 0.2 eq.) and *N*-bromosuccinimide (3.24 g, 18.19 mmol, 1.1 eq.) in acetonitrile (29 mL) and deionised water (1 mL) at room temperature. The reaction mixture was stirred for 17 hours at this temperature. The mixture was diluted with light petroleum (100 mL) and washed with NaHCO₃ (5% aq., 10 mL) and deionised water (2 x 10 mL). The organic layer was dried and the solvent removed under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography. Elution with 10% ethyl acetate/light petroleum afforded the bromide **248** as a colourless oil (2.48 g, 82%). The ¹H NMR spectrum matched the spectroscopic data provided by Kuang et al.²⁷⁵

¹H NMR (400 MHz, CDCl₃): δ 7.27–7.45 (5 H, m), 7.22 (1 H, d, *J* = 14.0 Hz), 6.86 (1 H, d, *J* = 14.0 Hz) ppm.

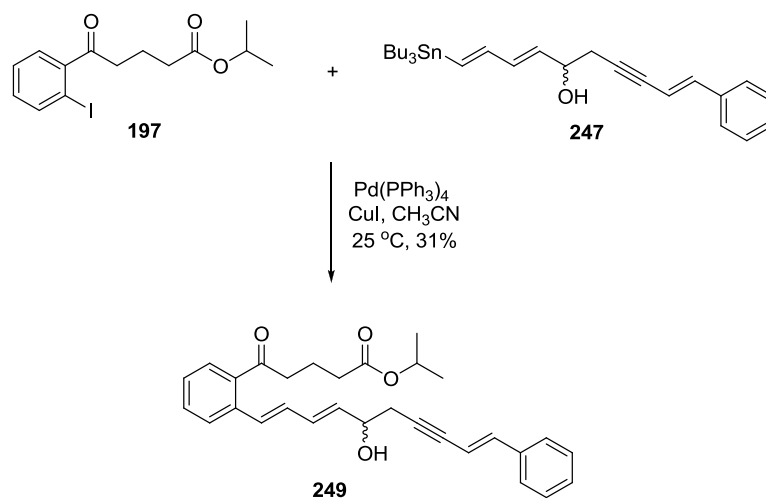
9.6.2 Sonogashira reaction between compound **209** and the bromide **248**



The bromide **248** (93 mg, 0.51 mmol, 1.0 eq.), Pd(PPh₃)₄ (41 mg, 0.04 mmol, 7 mol%), CuI (10 mg, 0.05 mmol, 10 mol%), piperidine (87 mg, 1.02 mmol, 2.0 eq.) and BHT (1 crystal) were added in one portion to compound **209** (209 mg, 0.51 mmol, 1.0 eq.) in degassed toluene (1 mL) and the mixture was stirred for 7 hours at room temperature. The mixture was diluted with ether (10 mL) and washed with deionised water (3 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 10% ethyl acetate/light petroleum afforded the stannane **247** as a colourless oil (136 mg, 52%).

¹H NMR (400 MHz, CDCl₃): δ 7.27–7.38 (5 H, m), 6.91 (1 H, d, *J* = 16.3 Hz), 6.54 (1 H, dd, *J* = 10.1, 18.6 Hz), 6.31 (1 H, d, *J* = 18.6 Hz), 6.28 (1 H, dd, *J* = 10.1, 15.5 Hz), 6.15 (1 H, dd, *J* = 2.2, 16.3 Hz), 5.74 (1 H, dd, *J* = 6.5, 15.5 Hz), 4.38 (1 H, m), 2.70 (1 H, ddd, *J* = 2.2, 5.4, 16.9 Hz), 2.64 (1 H, ddd, *J* = 2.2, 5.4, 16.9 Hz), 2.04 (1 H, d, *J* = 4.6 Hz), 1.47–1.52 (6 H, m), 1.25–1.37 (6 H, m), 0.85–0.95 (15 H, m) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 145.9 (CH), 141.2 (CH), 136.5 (C), 136.0 (CH), 134.7 (CH), 132.6 (CH), 128.8 (CH), 128.6 (CH), 126.3 (CH), 108.5 (CH), 88.1 (C), 82.5 (C), 70.8 (CH), 29.3 (CH₂), 29.1 (CH₂), 27.4 (CH₂), 13.8 (CH₃), 9.7 (CH₂) ppm; **ATR-FTIR**: 3400 (OH) cm⁻¹; **HRMS (ESI)**: [*M*⁺] C₂₈H₄₂OSn requires 513.2389; found: 513.2386.

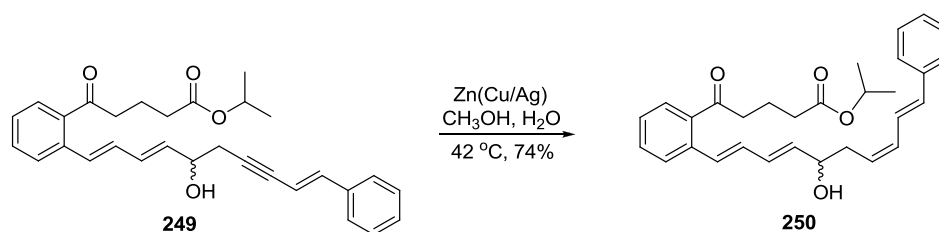
9.6.3 Stille reaction between the iodide **197** and the stannane **247**



The iodide **197** (128 mg, 0.35 mmol, 1.3 eq.), $\text{Pd(PPh}_3)_4$ (22 mg, 0.02 mmol, 7 mol%), CuI (6 mg, 0.03 mmol, 10 mol%) and BHT (1 crystal) were added to the stannane **247** (140 mg, 0.27 mmol, 1.0 eq.) in degassed acetonitrile (2 mL) and the reaction mixture was stirred for 3 days at room temperature. The mixture was diluted with ether (5 mL) and washed with deionised water (2 x 5 mL). The organic layer was dried and the solvent removed under reduced pressure to give a colourless liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 50% ethyl acetate/light petroleum afforded compound **249** as a yellow oil (39 mg, 31%, 95% brsm).

^1H NMR (400 MHz, CDCl_3): δ 7.58 (2 H, m), 7.43 (1 H, t, $J = 7.4$ Hz), 7.34 (2 H, m), 7.32 (2 H, m), 7.29 (2 H, m), 7.04 (1 H, d, $J = 15.4$ Hz), 6.93 (1 H, d, $J = 16.3$ Hz), 6.68 (1 H, dd, $J = 10.7, 15.4$ Hz), 6.52 (1 H, dd, $J = 10.7, 15.2$ Hz), 6.16 (1 H, dt, $J = 2.2, 16.3$ Hz), 5.94 (1 H, dd, $J = 6.3, 15.2$ Hz), 5.01 (1 H, sp, $J = 6.3$ Hz), 4.44 (1 H, m), 2.95 (2 H, t, $J = 7.2$ Hz), 2.74 (1 H, ddd, $J = 2.2, 5.5, 17.3$ Hz), 2.66 (1 H, ddd, $J = 2.2, 5.5, 17.3$ Hz), 2.37 (2 H, t, $J = 7.2$ Hz), 2.12 (1 H, d, $J = 4.6$ Hz), 2.03 (2 H, tt, $J = 7.2, 7.2$ Hz), 1.23 (6 H, d, $J = 6.3$ Hz) ppm;
 ^{13}C NMR (100 MHz, CDCl_3): δ 204.2 (C), 172.8 (C), 141.2 (CH), 137.8 (C), 136.7 (C), 136.5 (C), 135.3 (CH), 131.8 (CH), 131.6 (CH), 131.4 (CH), 131.1 (CH), 128.8 (CH), 128.6 (CH), 128.3 (CH), 127.4 (CH), 127.3 (CH), 126.3 (CH), 108.3 (CH), 88.0 (C), 82.6 (C), 70.8 (CH), 67.9 (CH), 41.0 (CH_2), 33.9 (CH_2), 29.1 (CH_2), 22.0 (CH_3), 19.8 (CH_2) ppm; **HRMS (ESI)**: $[\text{M}+23 (\text{Na})]^+$ $\text{C}_{30}\text{H}_{32}\text{O}_4$ requires 479.2198; found: 479.2198.

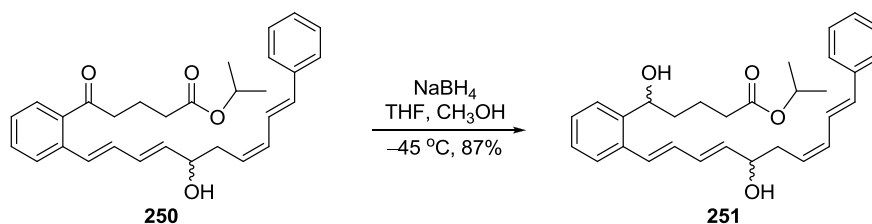
9.6.4 Reduction of the alkyne **249**



A Zn(Cu/Ag) amalgam²⁶⁵ (1.56 g, 100.7 eq.) was added in one portion to a nitrogen purged solution of compound **249** (30 mg, 0.07 mmol, 1.0 eq.) in methanol (3 mL) and deionised water (1 mL) at room temperature. The reaction mixture was heated at 42 °C for 21 hours. The mixture was filtered to remove the Zn(Cu/Ag) solid and the filtrate was concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 50% ethyl acetate/light petroleum afforded compound **250** as a colourless oil (22 mg, 74%).

¹H NMR (400 MHz, CDCl₃): δ 7.56 (2 H, m), 7.41 (3 H, m), 7.31 (3 H, m), 7.22 (1 H, d, J = 8.6 Hz), 7.06 (1 H, dd, J = 10.9, 15.6 Hz), 7.01 (1 H, d, J = 15.7 Hz), 6.66 (1 H, dd, J = 10.5, 15.7 Hz), 6.58 (1 H, d, J = 15.6 Hz), 6.48 (1 H, dd, J = 10.5, 15.2 Hz), 6.34 (1 H, t, J = 10.9 Hz), 5.90 (1 H, dd, J = 6.5, 15.2 Hz), 5.57 (1 H, dt, J = 7.7, 10.9 Hz), 5.01 (1 H, sp, J = 6.3 Hz), 4.35 (1 H, m), 2.95 (2 H, t, J = 7.2 Hz), 2.61 (2 H, m), 2.37 (2 H, t, J = 7.2 Hz), 2.03 (2 H, tt, J = 7.2, 7.2 Hz), 1.80 (1 H, d, J = 3.8 Hz), 1.23 (6 H, d, J = 6.3 Hz) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 204.1 (C), 172.7 (C), 137.6 (C), 137.3 (C), 136.6 (C), 136.5 (CH), 133.4 (CH), 131.8 (CH), 131.2 (CH), 131.1 (CH), 131.1 (CH), 131.0 (CH), 128.6 (CH), 128.2 (CH), 127.6 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 126.5 (CH), 124.0 (CH), 72.0 (CH), 67.7 (CH), 40.9 (CH₂), 35.9 (CH₂), 33.7 (CH₂), 21.8 (CH₃), 19.6 (CH₂) ppm; **HRMS (ESI)**: $[\text{M}+23 (\text{Na})]^+$ C₃₀H₃₄O₄ requires 481.2355; found: 481.2372.

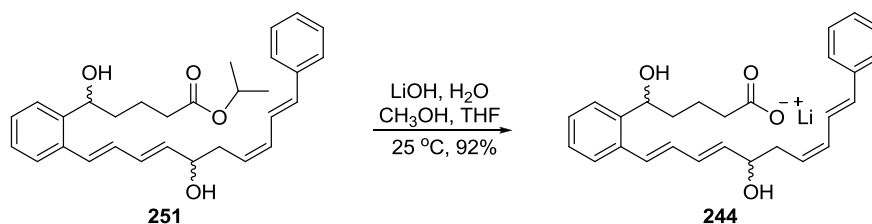
9.6.5 Reduction of the ketone **250**



NaBH₄ (4 mg, 0.10 mmol, 2.5 eq.) was added in small portions to compound **250** (18 mg, 0.04 mmol, 1.0 eq.) in tetrahydrofuran (2 mL) and methanol (1 mL) at –45 °C and the reaction mixture was stirred for 2 hours. The reaction was quenched with a saturated aqueous solution of NH₄Cl (2 mL) and the mixture was stirred for 30 minutes. The mixture was diluted with ethyl acetate (30 mL) and washed with deionised water (2 x 5 mL). The organic layer was dried and the solvent removed under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with 50% ethyl acetate/light petroleum afforded compound **251** as a colourless oil (16 mg, 87%).

¹H NMR (400 MHz, CDCl₃): δ 7.40–7.50 (4 H, m), 7.32 (3 H, m), 7.24 (2 H, m), 7.07 (1 H, dd, *J* = 11.0, 15.6 Hz), 6.90 (1 H, d, *J* = 15.2 Hz), 6.57 (1 H, dd, *J* = 10.4, 15.2 Hz), 6.59 (1 H, d, *J* = 15.6 Hz), 6.49 (1 H, dd, *J* = 10.4, 15.2 Hz), 6.36 (1 H, t, *J* = 11.0 Hz), 5.90 (1 H, dd, *J* = 6.3, 15.2 Hz), 5.58 (1 H, dt, *J* = 7.7, 11.0 Hz), 5.02 (1 H, m), 5.00 (1 H, sp, *J* = 6.3 Hz), 4.36 (1 H, m), 2.63 (2 H, m), 2.32 (2 H, t, *J* = 7.2 Hz), 1.99 (1 H, br. s), 1.68–1.79 (4 H, m), 1.76 (1 H, br. s), 1.22 (6 H, d, *J* = 6.3 Hz) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 173.3 (C), 141.8 (C), 137.5 (C), 136.1 (CH), 134.9 (C), 133.6 (CH), 132.0 (CH), 131.2 (CH), 130.7 (CH), 129.7 (CH), 128.8 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 127.1 (CH), 126.6 (CH), 126.1 (CH), 125.8 (CH), 124.1 (CH), 72.2 (CH), 70.6 (CH), 67.8 (CH), 37.8 (CH₂), 36.2 (CH₂), 34.5 (CH₂), 22.0 (CH₃), 21.6 (CH₂) ppm; **HRMS (ESI)**: [M+23 (Na)]⁺ C₃₀H₃₆O₄ requires 483.2511; found: 483.2509.

9.6.6 Synthesis of the C₁₈-phenyl analogue 244

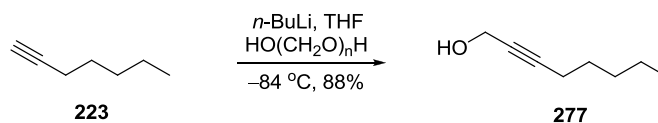


LiOH (2 mg, 0.07 mmol, 3.0 eq.) was added in one portion to a solution of compound **251** (10 mg, 0.02 mmol, 1.0 eq.) in tetrahydrofuran (0.5 mL), methanol (0.2 mL) and deionised water (0.2 mL) and the reaction mixture was stirred at room temperature for 3 hours. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford the target compound **244** as a yellow oil (8 mg, 92%).

¹H NMR (400 MHz, CDCl₃): δ 7.41–7.49 (4 H, m), 7.29 (2 H, t, *J* = 7.3 Hz), 7.19 (3 H, m), 7.16 (1 H, dd, *J* = 10.9, 15.6 Hz), 6.96 (1 H, d, *J* = 15.0 Hz), 6.67 (1 H, dd, *J* = 10.6, 15.0 Hz), 6.56 (1 H, d, *J* = 15.6 Hz), 6.49 (1 H, dd, *J* = 10.6, 15.2 Hz), 6.28 (1 H, t, *J* = 10.9 Hz), 5.89 (1 H, dd, *J* = 6.5, 15.2 Hz), 5.60 (1 H, dt, *J* = 7.9, 10.9 Hz), 5.00 (1 H, m), 4.27 (1 H, m), 2.60 (2 H, m), 2.20 (2 H, m), 1.68–1.75 (3 H, m), 1.63 (1 H, m) ppm; **¹³C NMR** (100 MHz, CDCl₃): δ 182.7 (C), 143.7 (C), 139.0 (C), 137.5 (CH), 136.1 (C), 133.9 (CH), 132.3 (CH), 132.2 (CH), 131.9 (CH), 131.6 (CH), 130.7 (CH), 129.7 (CH), 128.9 (CH), 128.5 (CH), 128.0 (CH), 127.4 (CH), 127.0 (CH), 126.6 (CH), 125.5 (CH), 73.2 (CH), 71.0 (CH), 39.8 (CH₂), 38.9 (CH₂), 37.0 (CH₂), 24.1 (CH₂) ppm; **ATR-FTIR**: 3382 (OH) and 1587 (C=O) cm⁻¹; **HRMS (ESI)**: [M+23 (Na)]⁺ C₂₇H₂₉LiO₄ requires 425.2304; found: 425.2324; **UV spectrum**: λ_{max} (log ε) = 281 (3.59) nm in MeOH.

9.7 Chapter 7 experimental procedures

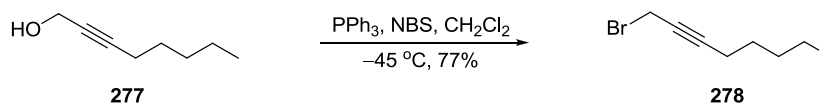
9.7.1 Preparation of oct-2-yn-1-ol



Following the procedure by Wu and co-workers,³¹⁴ *n*-BuLi (1.6 M in hexanes, 32.5 mL, 0.05 mol, 1.0 eq.) was added dropwise to 1-heptyne (5.00 g, 0.05 mol, 1.0 eq.) in anhydrous tetrahydrofuran (50 mL) at $-84\text{ }^{\circ}\text{C}$. The solution was stirred for 1 hour at this temperature after which small portions of paraformaldehyde (1.56 g, 0.05 mol, 1.0 eq.) were added. The reaction mixture was allowed to warm to room temperature and stirred for 12 hours. The reaction was quenched with deionised water (10 mL) and the mixture was stirred for 30 minutes. The mixture was diluted with ether (40 mL) and washed with deionised water (2 x 10 mL). The organic layer was dried and concentrated under reduced pressure to give a yellow liquid. The liquid was subjected to column chromatography. Elution with 20% ethyl acetate/light petroleum afforded the alcohol **277** as a yellow oil (5.78 g, 88%). The ^1H NMR spectrum matched that reported in the literature.³¹⁴

^1H NMR (400 MHz, CDCl_3): δ 4.17 (2 H, s), 2.89 (1 H, br. s), 2.13 (2 H, ddd, $J = 2.2, 7.1, 14.3\text{ Hz}$), 1.44 (2 H, m), 1.26 (4 H, m), 0.83 (3 H, t, $J = 7.0\text{ Hz}$).

9.7.2 Synthesis of 1-bromo-2-octyne

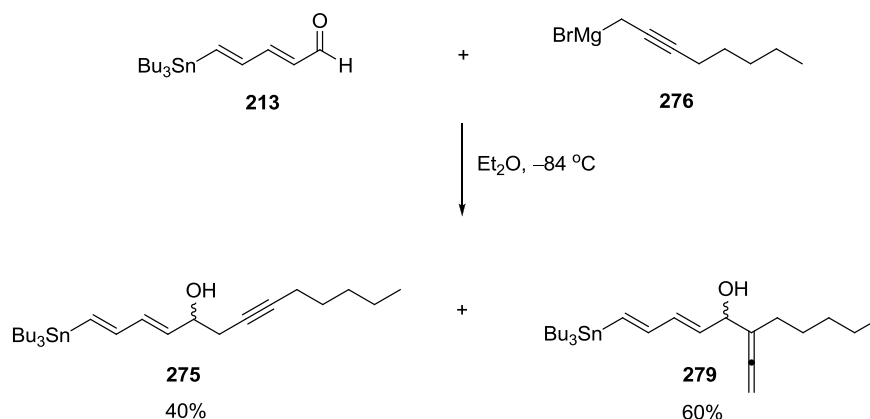


Triphenylphosphine (1.14 g, 4.36 mmol, 1.1 eq.) and *N*-bromosuccinimide (776 mg, 4.36 mmol, 1.1 eq.) were added successively to the alcohol **277** (0.50 g, 3.96 mmol, 1.0 eq.) in anhydrous dichloromethane (25 mL) at $-45\text{ }^{\circ}\text{C}$. The mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$ and was stirred for 2 hours. The reaction mixture was then washed with deionised water (3 x 10 mL). The organic layer was dried and concentrated under reduced pressure to afford a purple solid. The solid was subjected to column chromatography. Elution with light petroleum afforded the bromide **278** as a

colourless oil (577 mg, 77%). The ^1H NMR spectrum matched that reported in the literature.²⁸⁷

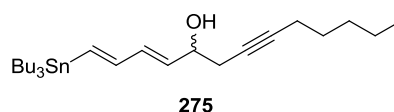
^1H NMR (400 MHz, CDCl_3): δ 3.92 (2 H, t, $J = 2.3$ Hz), 2.22 (2 H, ddd, $J = 2.3$, 7.1, 14.3 Hz), 1.50 (2 H, m), 1.32 (4 H, m), 0.89 (3 H, t, $J = 7.1$ Hz) ppm.

9.7.3 Addition of the Grignard reagent **276** to compound **213**



The bromide **278** (885 mg, 4.68 mmol, 1.1 eq.) was added in one portion to a mixture of magnesium turnings (207 mg, 8.51 mmol, 2.0 eq.), iodine (27 mg, 0.21 mmol) and HgCl_2 (58 mg, 0.21 mmol) in anhydrous ether (5 mL) at 0°C . The reaction mixture was stirred for two hours at this temperature then cooled to -84°C . Compound **213** (1.58 g, 4.26 mmol, 1.0 eq.) in anhydrous ether (3 mL) was added dropwise and the mixture was stirred for two and a half hours. A saturated aqueous solution of NH_4Cl (5 mL) was then added dropwise. The mixture was diluted with ether (30 mL) and washed with deionised water (2 x 10 mL). The ethereal layer was dried and concentrated under reduced pressure to afford a yellow oil that was a mixture of the stannane **275** (0.82 g, 40%) and the stannane **279** (1.23 g, 60%). Attempts to purify the products by column chromatography proved difficult.

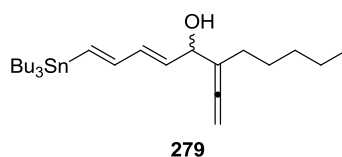
Compound **275**:



^1H NMR (400 MHz, CDCl_3): δ 6.52 (1 H, dd, $J = 10.1$, 18.5 Hz), 6.26 (1 H, d, $J = 18.5$ Hz), 6.26 (1 H, dd, $J = 10.1$, 15.7 Hz), 5.69 (1 H, dd, $J = 6.4$, 15.7 Hz), 4.33 (1

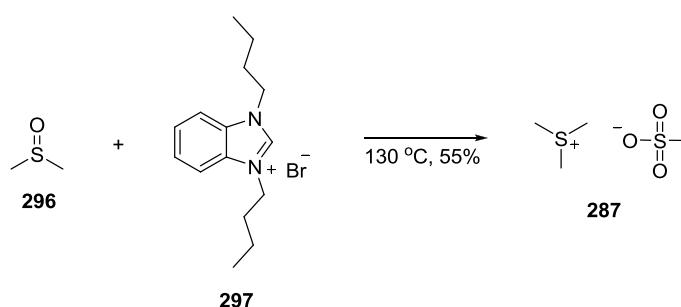
H, m), 2.46 (1 H, dddd, $J = 2.4, 2.5, 7.0, 16.4$ Hz), 2.41 (1 H, dddd, $J = 2.4, 2.5, 7.0, 16.4$ Hz), 2.17 (2 H, ddd, $J = 2.4, 7.0, 14.2$ Hz), 2.04 (1 H, d, $J = 4.7$ Hz), 1.46–1.51 (7 H, m), 1.25–1.44 (11 H, m), 0.93–0.97 (18 H, m) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 146.0 (CH), 135.5 (CH), 134.4 (CH), 132.9 (CH), 83.8 (C), 75.7 (C), 70.8 (CH), 31.2 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 28.3 (CH_2), 27.4 (CH_2), 22.4 (CH_2), 18.9 (CH_2), 14.2 (CH_3), 13.8 (CH_3), 9.7 (CH_2) ppm; ATR-FTIR: 3375 (OH) cm^{-1} ; HRMS (ESI): $[\text{M}+23 (\text{Na})]^+$ $\text{C}_{25}\text{H}_{46}\text{OSn}$ requires 481.2643; found: 481.2648.

Compound **279**:



^1H NMR (400 MHz, CDCl_3): δ 6.52 (1 H, dd, $J = 9.7, 18.6$ Hz), 6.29 (1 H, d, $J = 18.6$ Hz), 6.16 (1 H, dd, $J = 9.7, 15.2$ Hz), 5.61 (1 H, dd, $J = 7.3, 15.2$ Hz), 4.93 (2 H, m), 4.52 (1 H, m), 1.95 (2 H, m), 1.80 (1 H, d, $J = 4.7$ Hz), 1.43–1.52 (6 H, m), 1.26–1.36 (12 H, m), 0.87–0.98 (18 H, m) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 204.2 (C), 146.0 (CH), 135.5 (CH), 134.7 (CH), 132.4 (CH), 107.5 (C), 79.7 (CH_2), 72.6 (CH), 58.6 (CH_2), 31.7 (CH_2), 29.3 (CH_2), 27.4 (CH_2), 22.7 (CH_2), 18.6 (CH_3), 17.7 (CH_2), 13.8 (CH_2), 9.7 (CH_3) ppm; HRMS (ESI): Molecular ion not found.

9.7.4 Preparation of trimethylsulfonium methanesulfonate

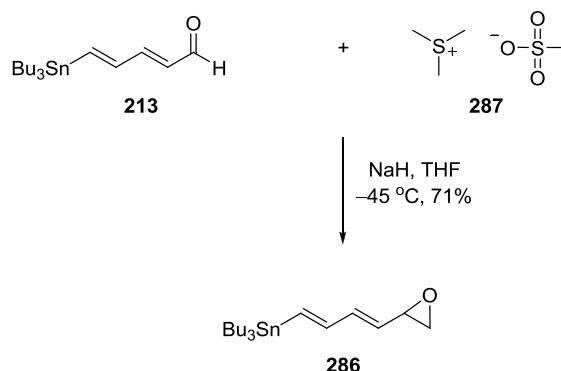


A solution of dimethylsulfoxide (752 mg, 9.63 mmol, 3.0 eq.) and dibutylbenzimidazolium bromide **297** (1.00 g, 3.21 mmol, 1.0 eq.) was heated in air for 3 days at 130 °C. The reaction mixture was cooled to 0 °C. Ethanol (4 mL) and ether (60 mL) were then added in one portion. The resulting suspension was filtered and the precipitate titrated with cold ethanol to afford trimethylsulfonium

methanesulfonate as white crystals (304 mg, 55%). The ^1H NMR spectrum matched that reported by Travers.²⁹⁹

^1H NMR (400 MHz, D_2O): δ 2.94 (9 H, s), 2.84 (3 H, s) ppm.

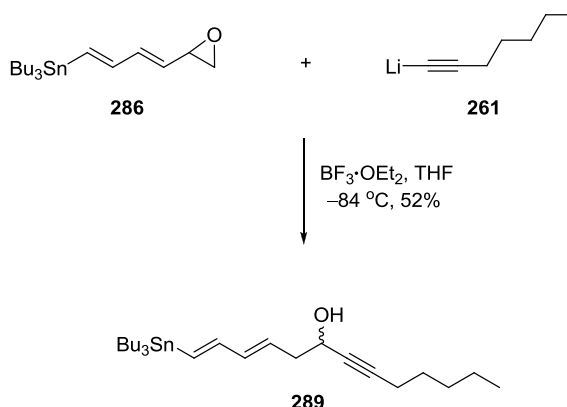
9.7.5 Synthesis of the epoxide **286**



To a solution of trimethylsulfonium methanesulfonate (0.10 g, 0.58 mmol, 1.2 eq.) in anhydrous tetrahydrofuran (2 mL) was added 60% NaH in mineral oil (23 mg, 0.58 mmol, 1.2 eq.) at 0 °C. The reaction mixture was stirred for 10 minutes then cooled to -45 °C and the aldehyde **213** (0.18 g, 0.48 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (2 mL) was added dropwise. The reaction mixture was stirred for 4 hours. The reaction was then quenched with a saturated aqueous solution of NH_4Cl (3 mL) and the mixture was stirred for 30 minutes. The reaction mixture was diluted with light petroleum (40 mL), washed with deionised water (2 x 20 mL), dried and concentrated under reduced pressure to give a brown oil. The oil was subjected to column chromatography and the column was conditioned with triethylamine (1%). Elution with light petroleum afforded the epoxide **286** as a colourless liquid (133 mg, 71%).

^1H NMR (400 MHz, CDCl_3): δ 6.53 (1 H, dd, J = 9.9, 18.6 Hz), 6.43 (1 H, dd, J = 6.5, 14.9 Hz), 6.31 (1 H, d, J = 18.6 Hz), 5.30 (1 H, dd, J = 9.9, 14.9 Hz), 3.36 (1 H, m), 2.99 (1 H, dd, J = 4.1, 5.3 Hz), 2.68 (1 H, dd, J = 2.6, 5.3 Hz), 1.47–1.52 (6 H, m), 1.25–1.35 (6 H, m), 0.81–0.93 (15 H, m) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 145.4 (CH), 138.0 (CH), 136.4 (CH), 129.1 (CH), 52.4 (CH), 49.4 (CH_2), 29.2 (CH_2), 27.4 (CH_2), 13.8 (CH_3), 9.7 (CH_2) ppm; HRMS (ESI): Molecular ion not found.

9.7.6 Synthesis of the stannane **289**



n-BuLi (1.6 M in hexanes, 58 μL , 0.09 mmol, 1.2 eq.) was added dropwise to 1-hexyne (7 mg, 0.08 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (2 mL) at -84°C . The solution was stirred for 1 hour at this temperature after which the epoxide **286** (30 mg, 0.08 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (2 mL) was added in one portion. The reaction mixture was stirred for 5 minutes followed by the dropwise addition of $\text{BF}_3 \cdot \text{OEt}_2$ (11 mg, 0.08 mol, 1.0 eq.) at this temperature. After 30 minutes, the reaction was quenched with a saturated aqueous solution of NH_4Cl (2 mL) and the mixture was stirred for a further 30 minutes. The reaction mixture was diluted with ether (10 mL), washed with deionised water (2 x 5 mL), dried and concentrated under reduced pressure to give an orange liquid. The liquid was subjected to column chromatography. Elution with 10% ethyl acetate/light petroleum afforded the stannane **289** as a colourless oil (20 mg, 52%).

^1H NMR (400 MHz, CDCl_3): δ 6.52 (1 H, dd, $J = 11.0, 18.6$ Hz), 6.17 (1 H, d, $J = 18.6$ Hz), 6.16 (1 H, dd, $J = 11.0, 15.2$ Hz), 5.70 (1 H, dt, $J = 7.3, 15.2$ Hz), 4.41 (1 H, m), 2.48 (2 H, t, $J = 7.3$ Hz), 2.12 (2 H, t, $J = 7.1$ Hz), 1.80 (1 H, d, $J = 5.9$ Hz), 1.47–1.52 (7 H, m), 1.26–1.35 (11 H, m), 0.85–0.96 (18 H, m) ppm; **^{13}C NMR** (100 MHz, CDCl_3): δ 146.6 (CH), 137.6 (CH), 133.3 (CH), 127.4 (CH), 86.3 (C), 80.8 (C), 62.3 (CH), 41.5 (CH_2), 31.2 (CH_2), 29.3 (CH_2), 28.5 (CH_2), 27.4 (CH_2), 22.3 (CH_2), 18.8 (CH_2), 14.1 (CH_3), 13.8 (CH_3), 9.6 (CH_2) ppm; **ATR-FTIR**: 3320 (OH) cm^{-1} ; **HRMS (ESI)**: $[\text{M}+23(\text{Na})]^+$ $\text{C}_{25}\text{H}_{46}\text{OSn}$ requires 481.2643; found: 481.2648.

Chapter 10

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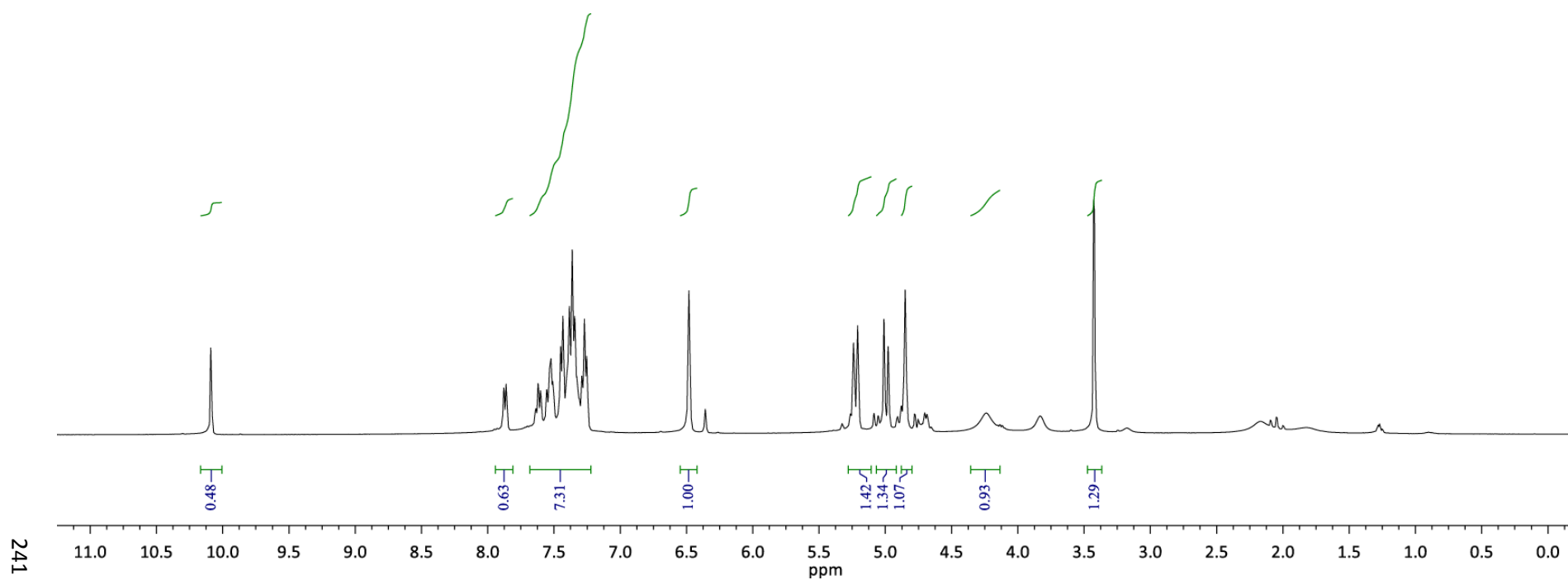
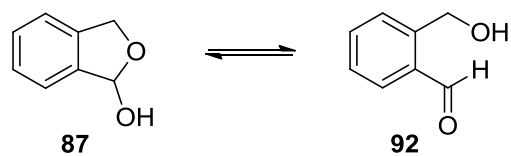
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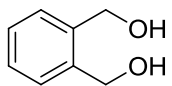
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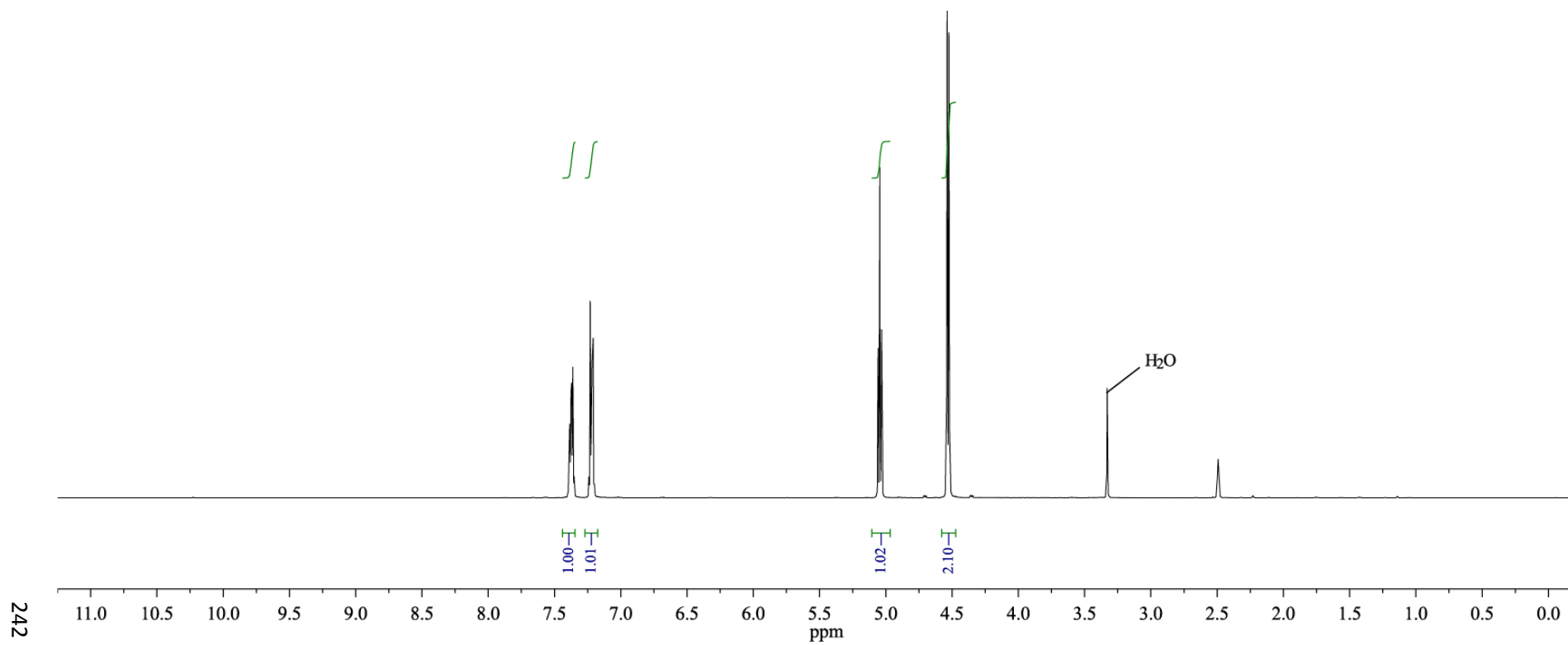
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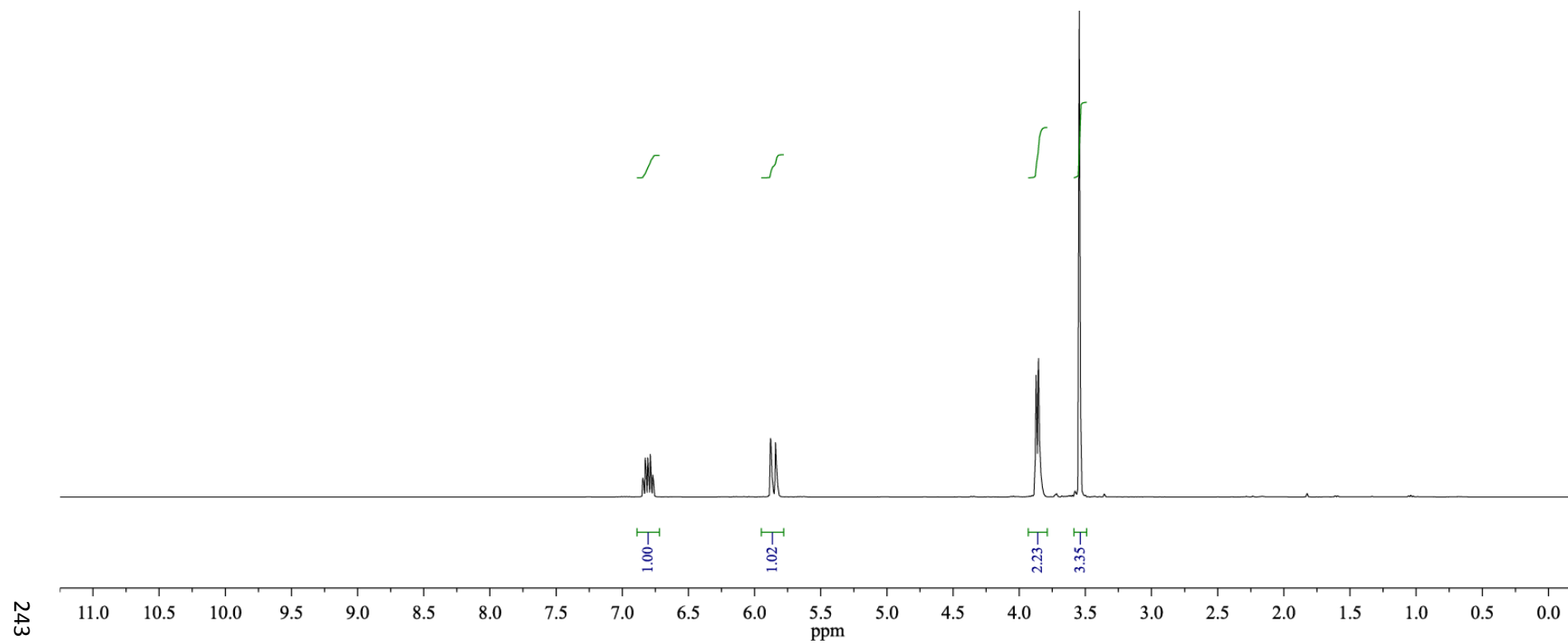
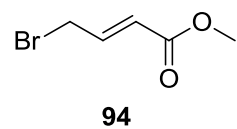
Appendix A - Chapter 2 spectra

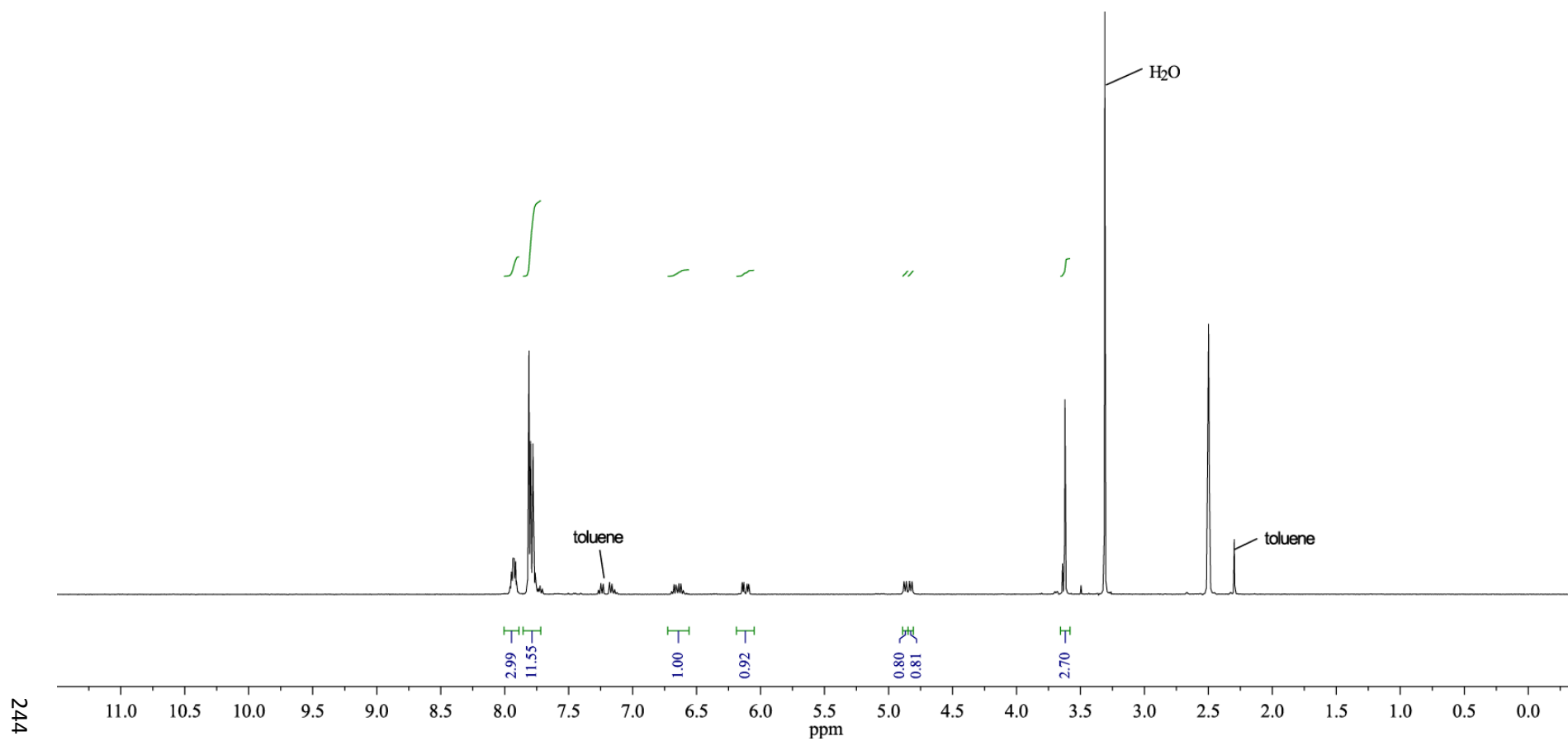
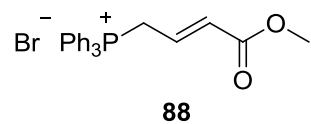


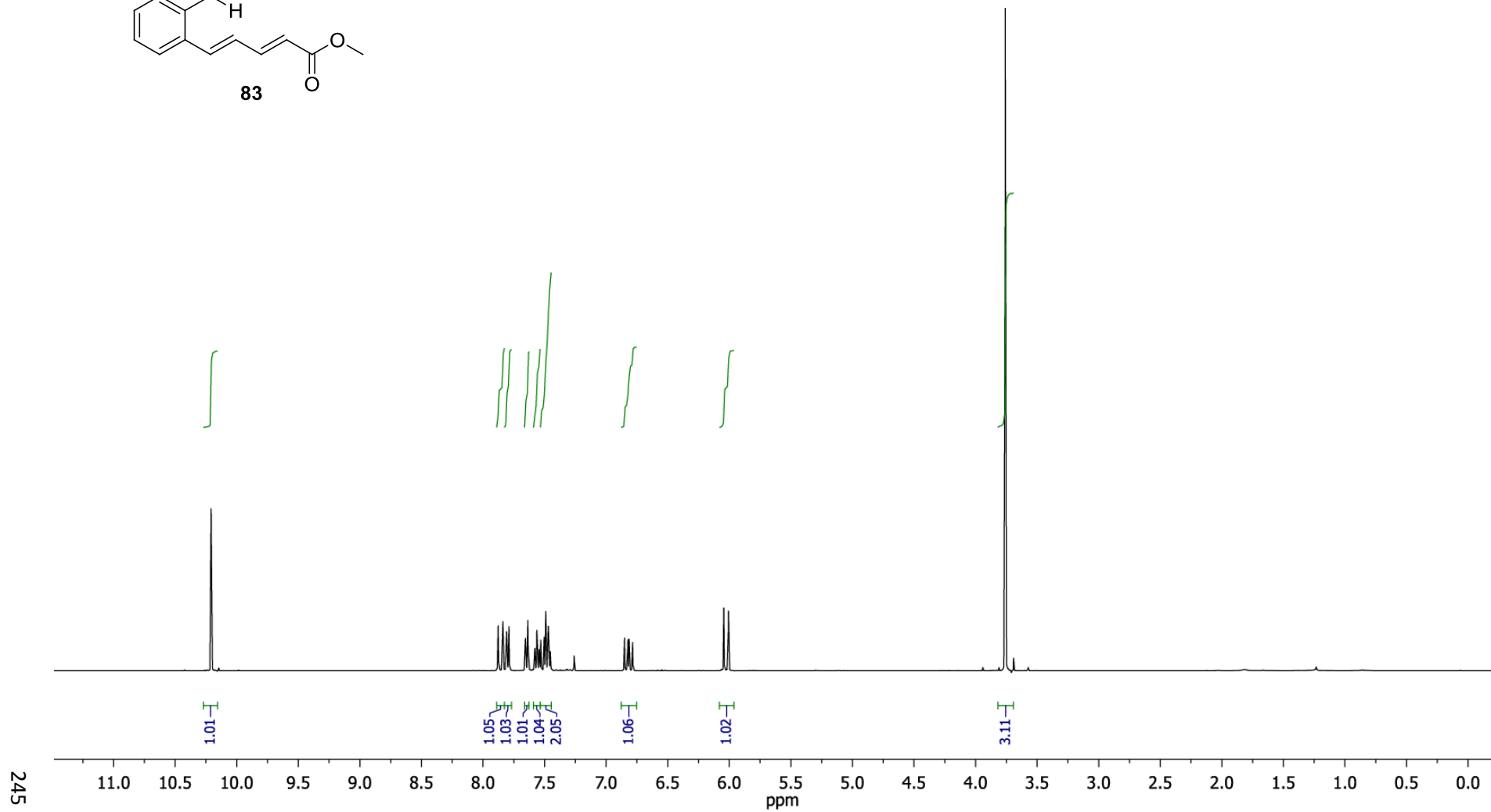
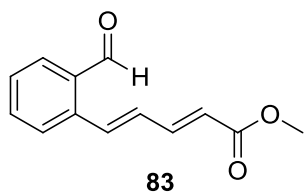


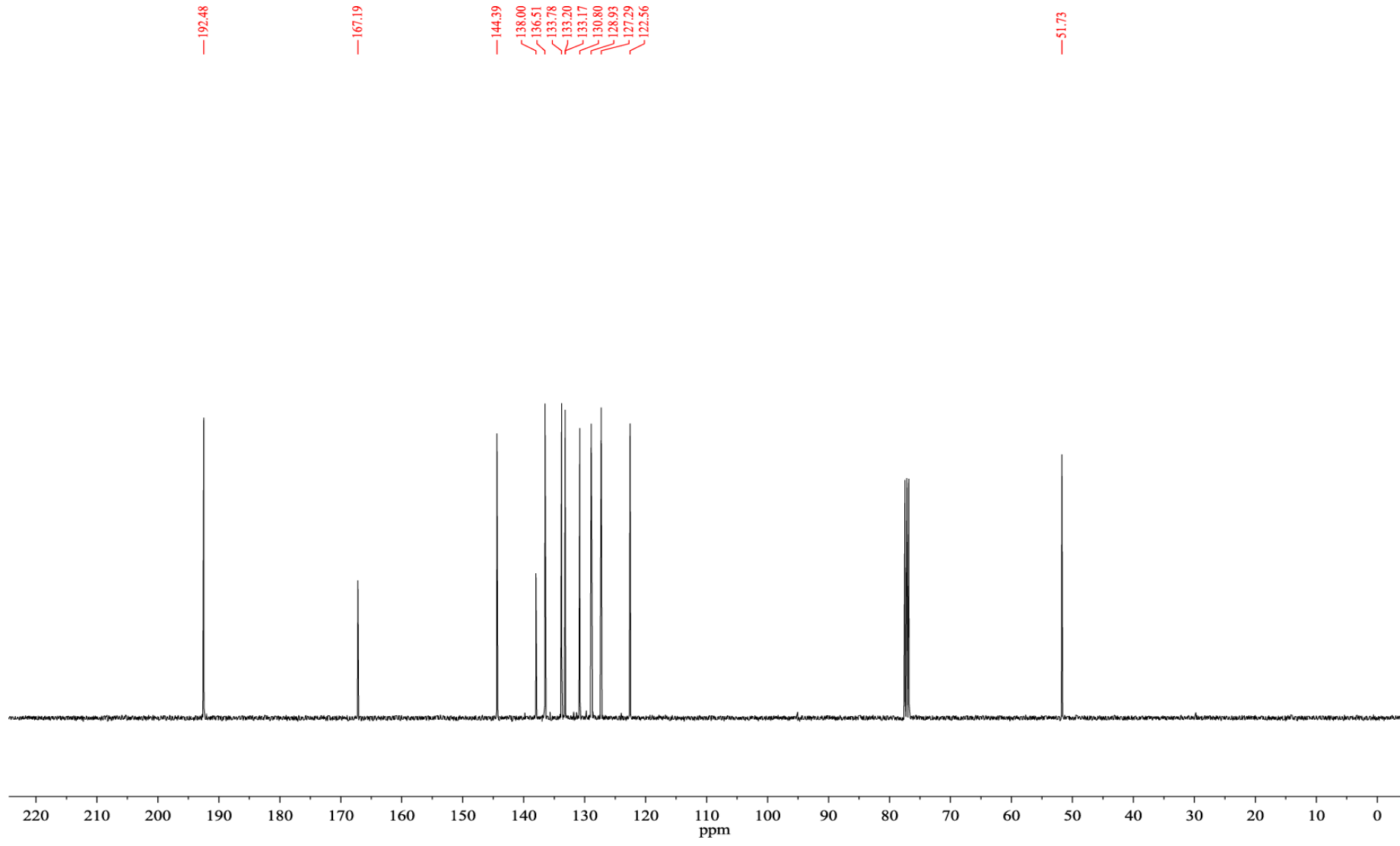
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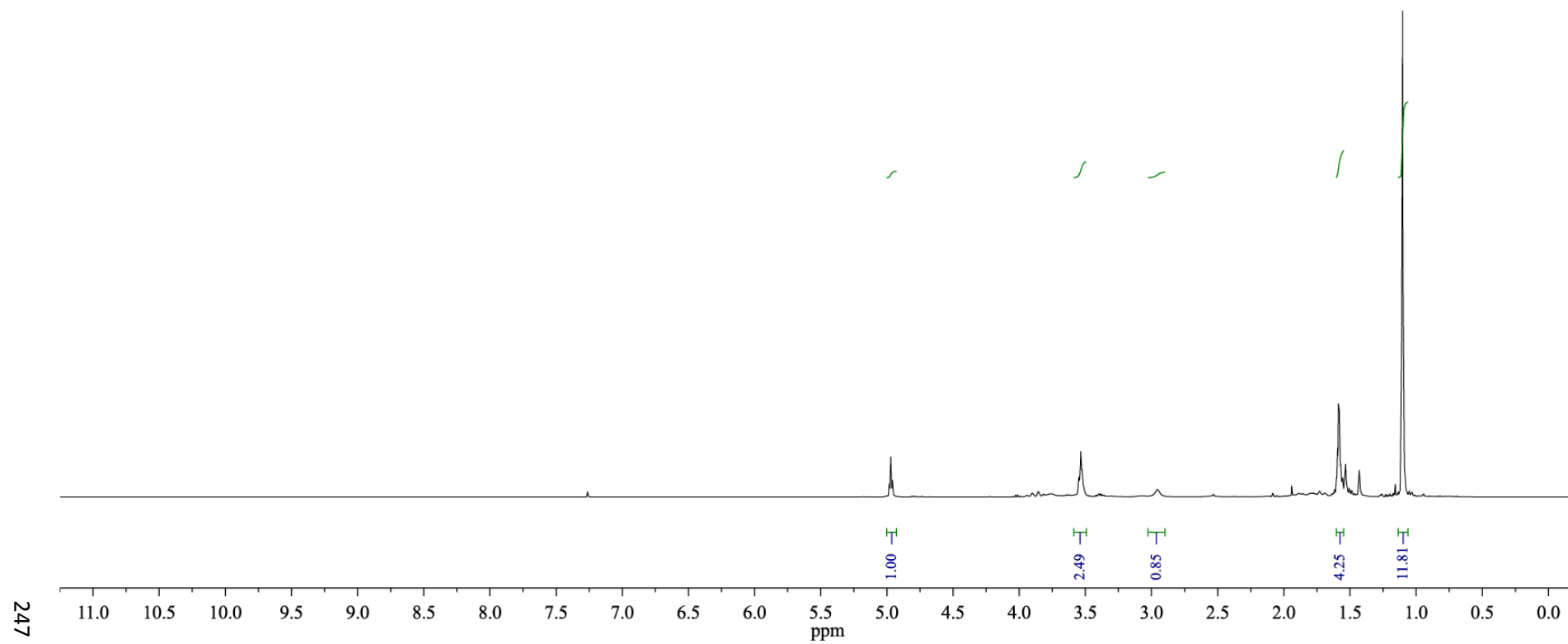
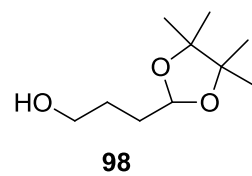


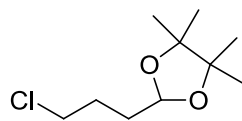




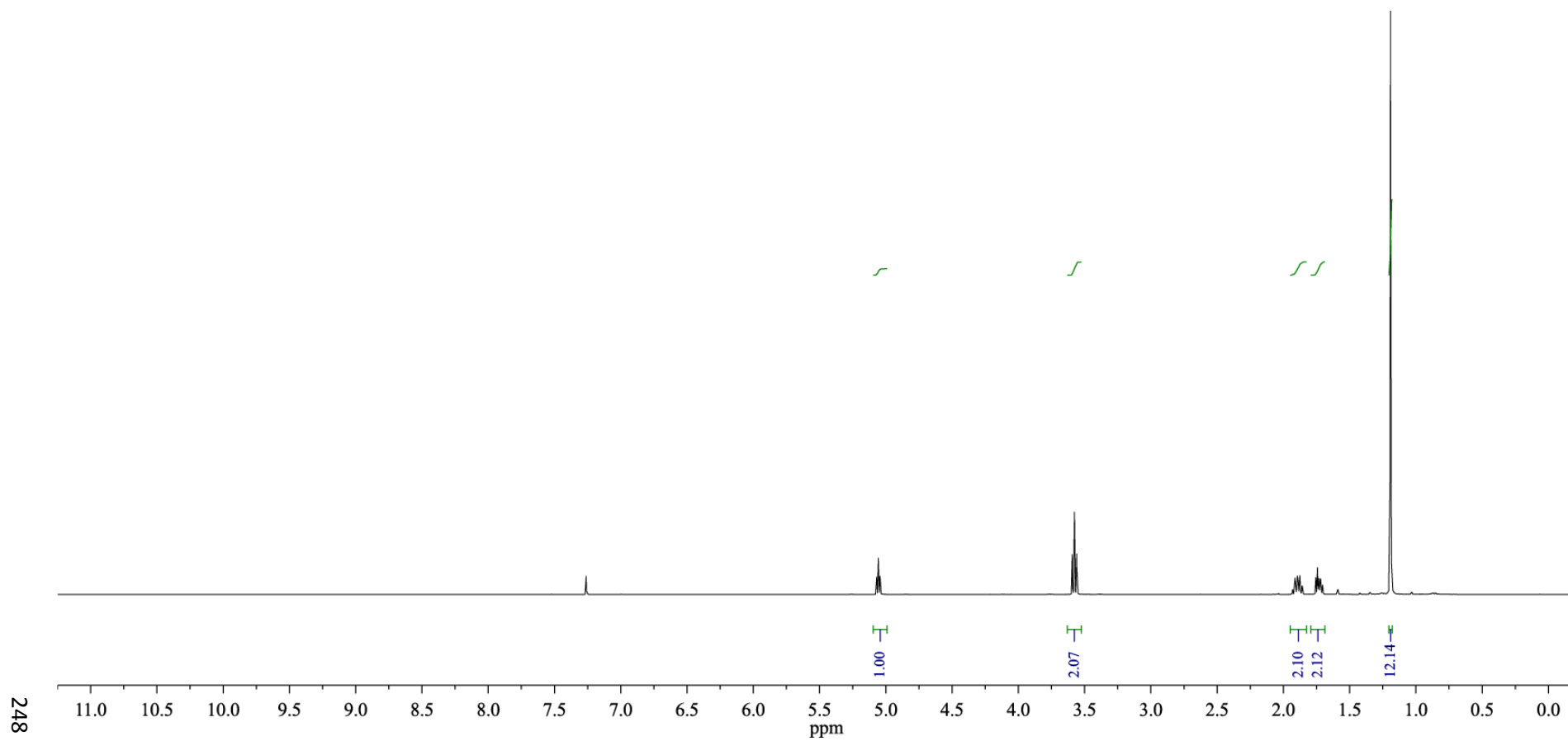


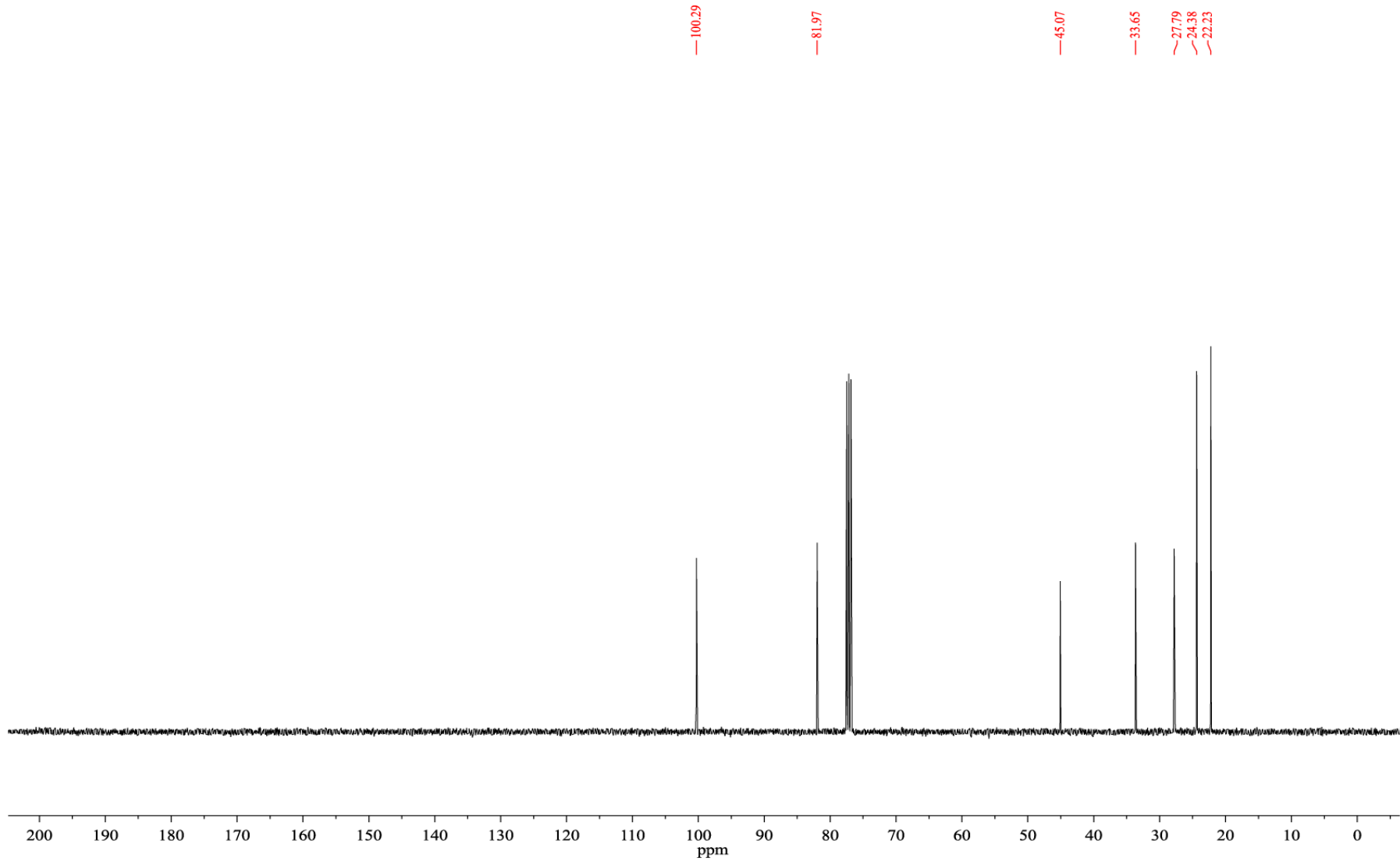


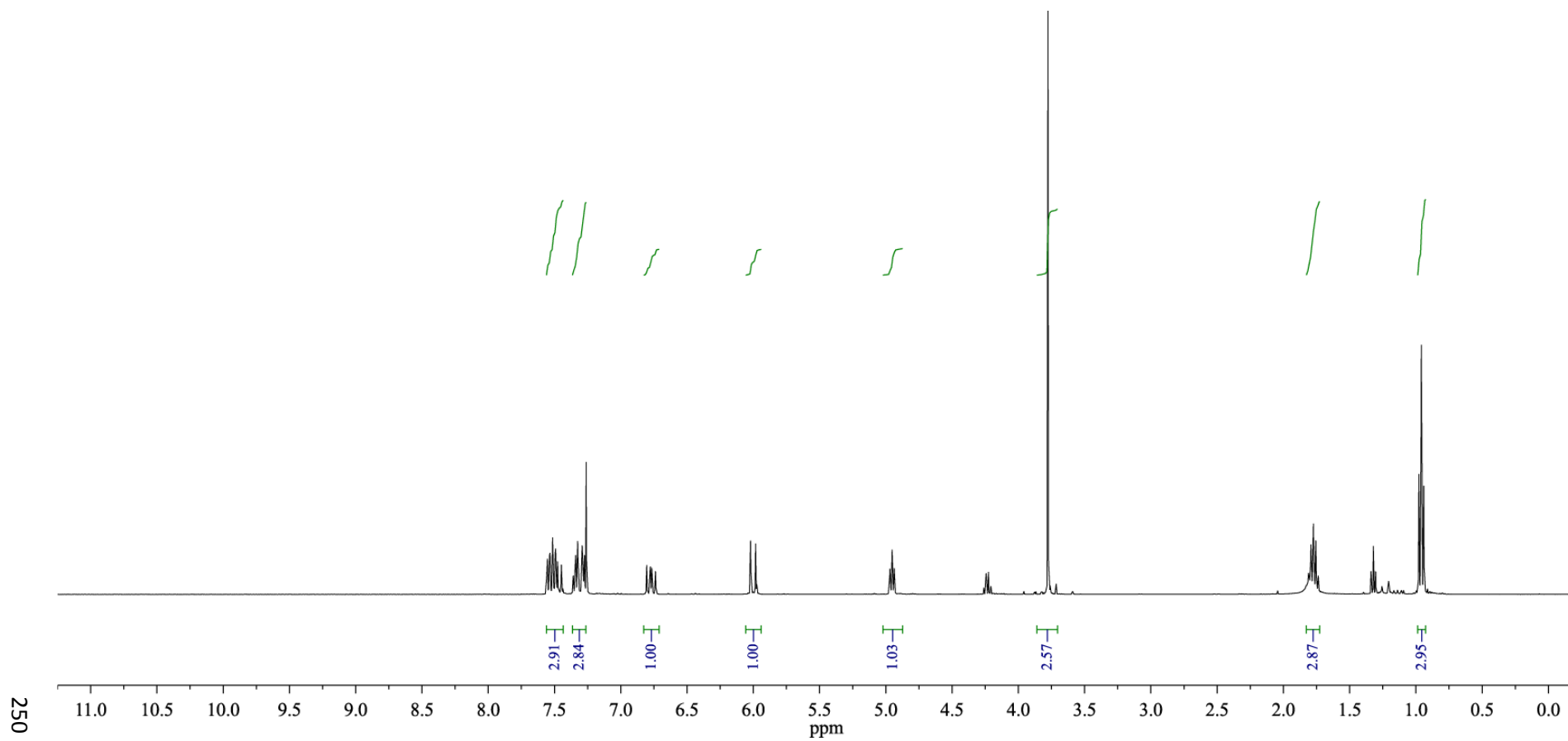
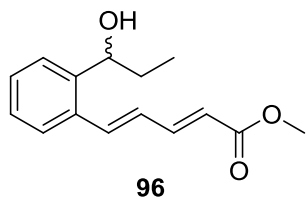


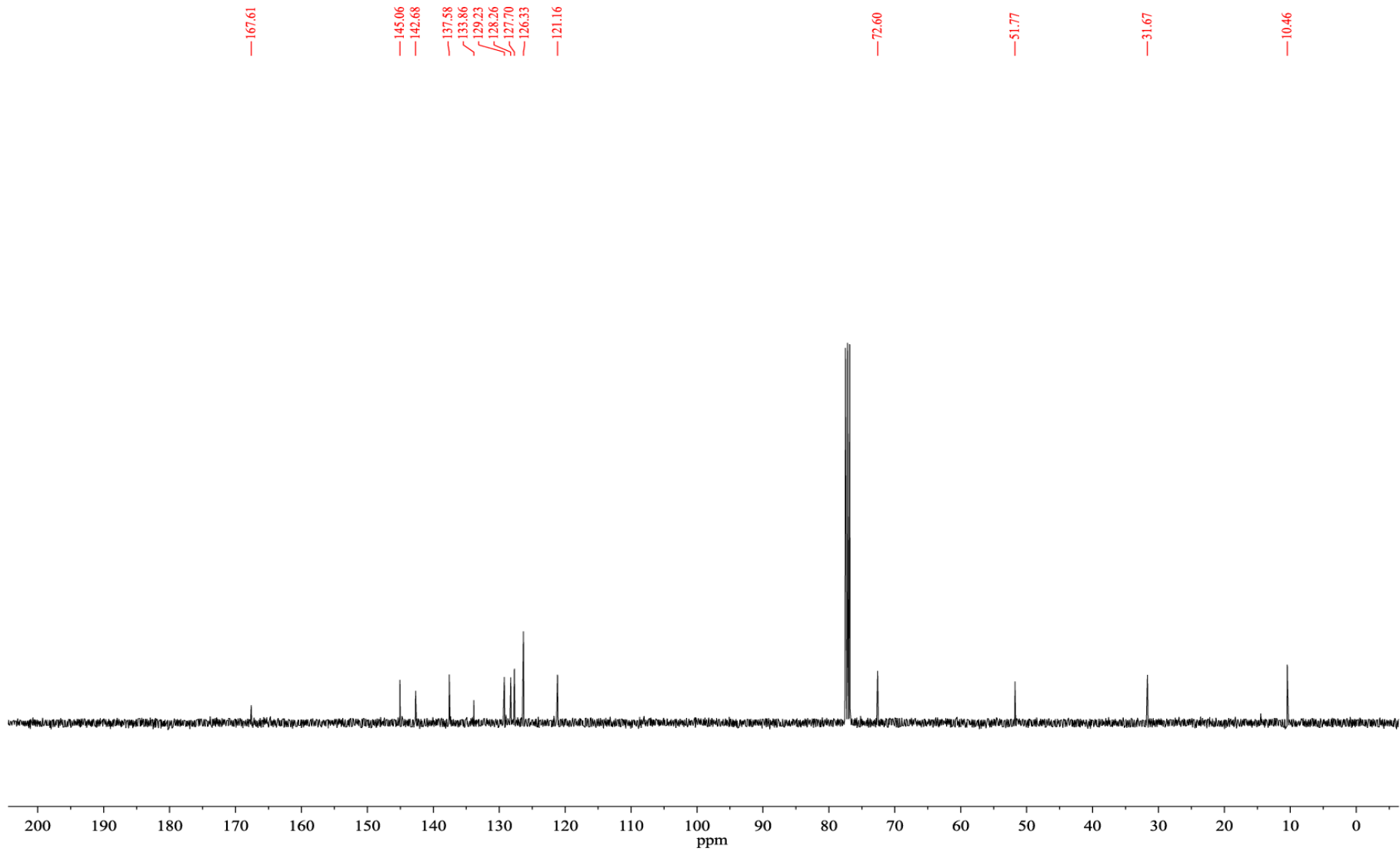


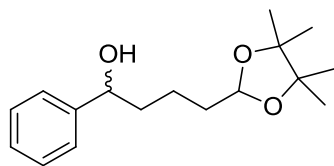
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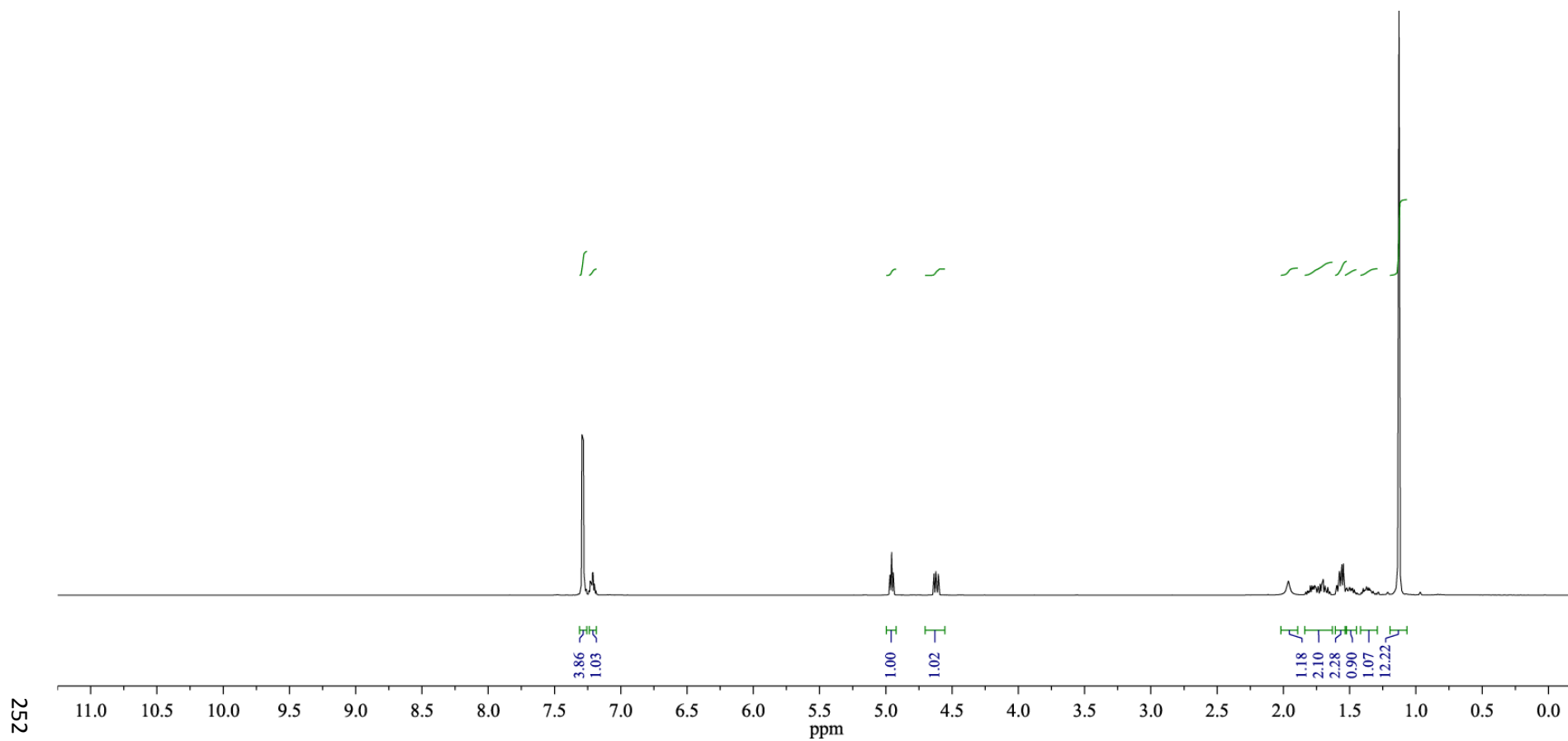


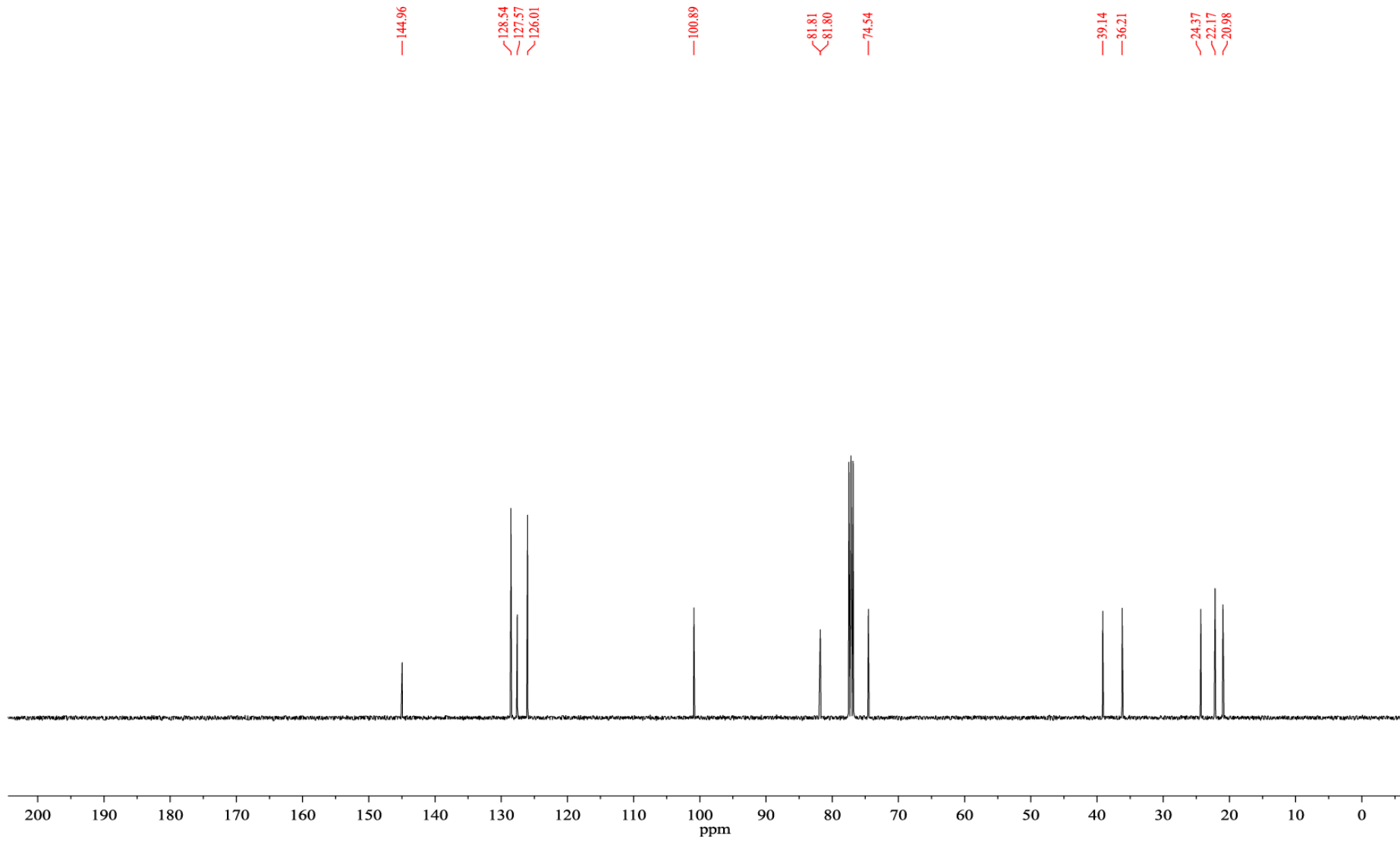


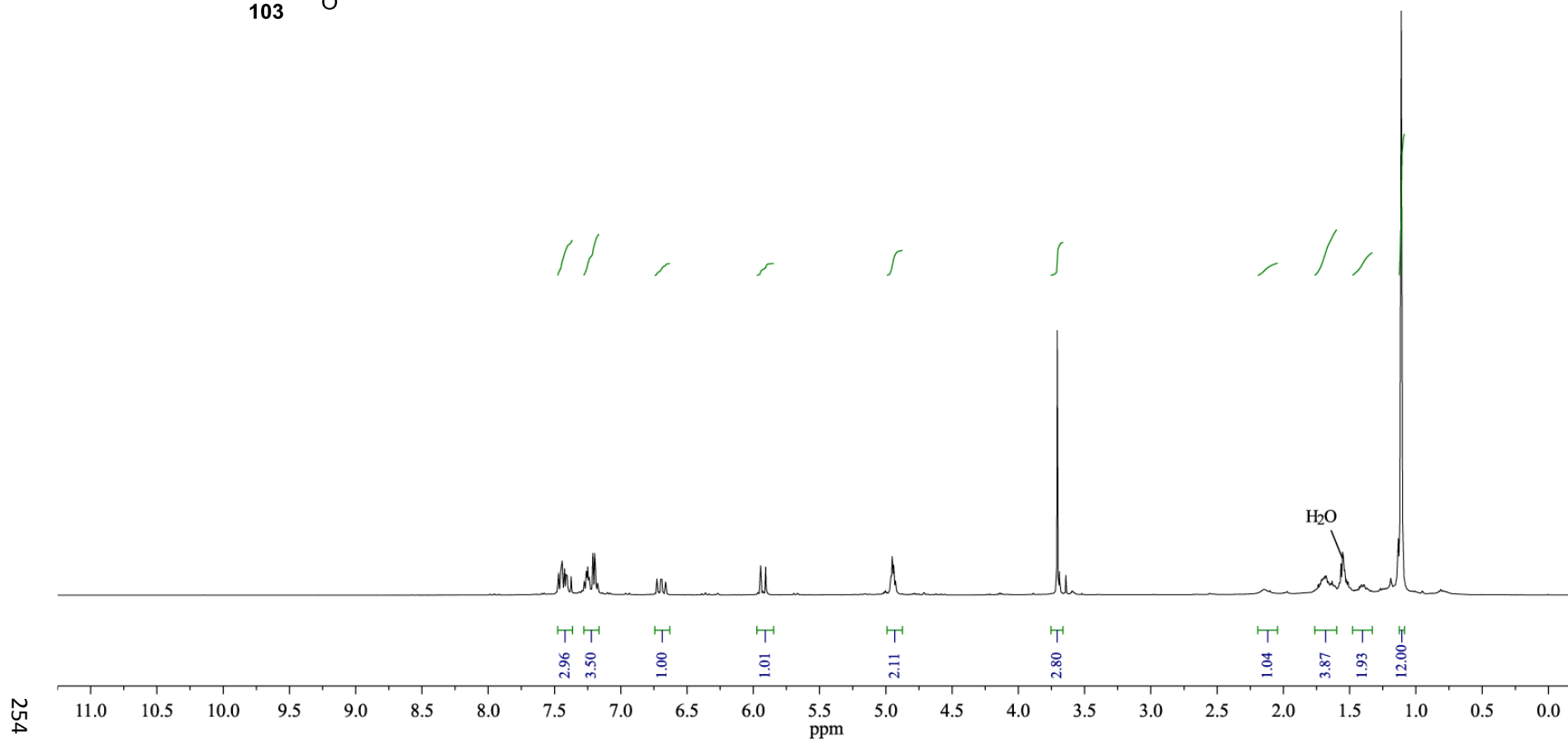
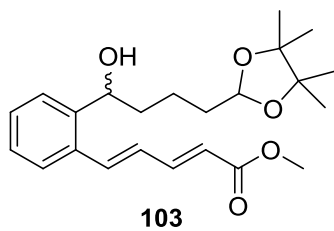


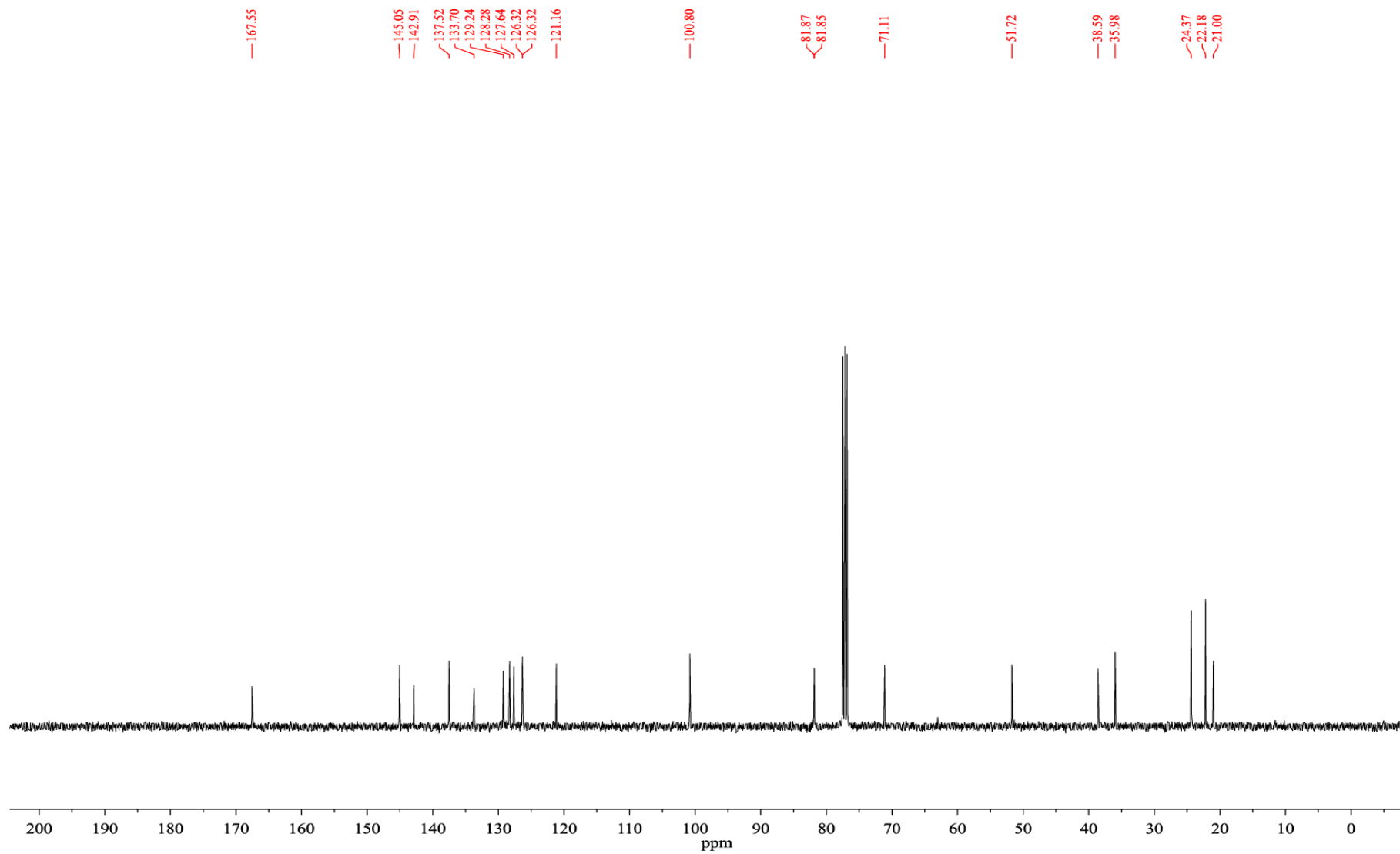


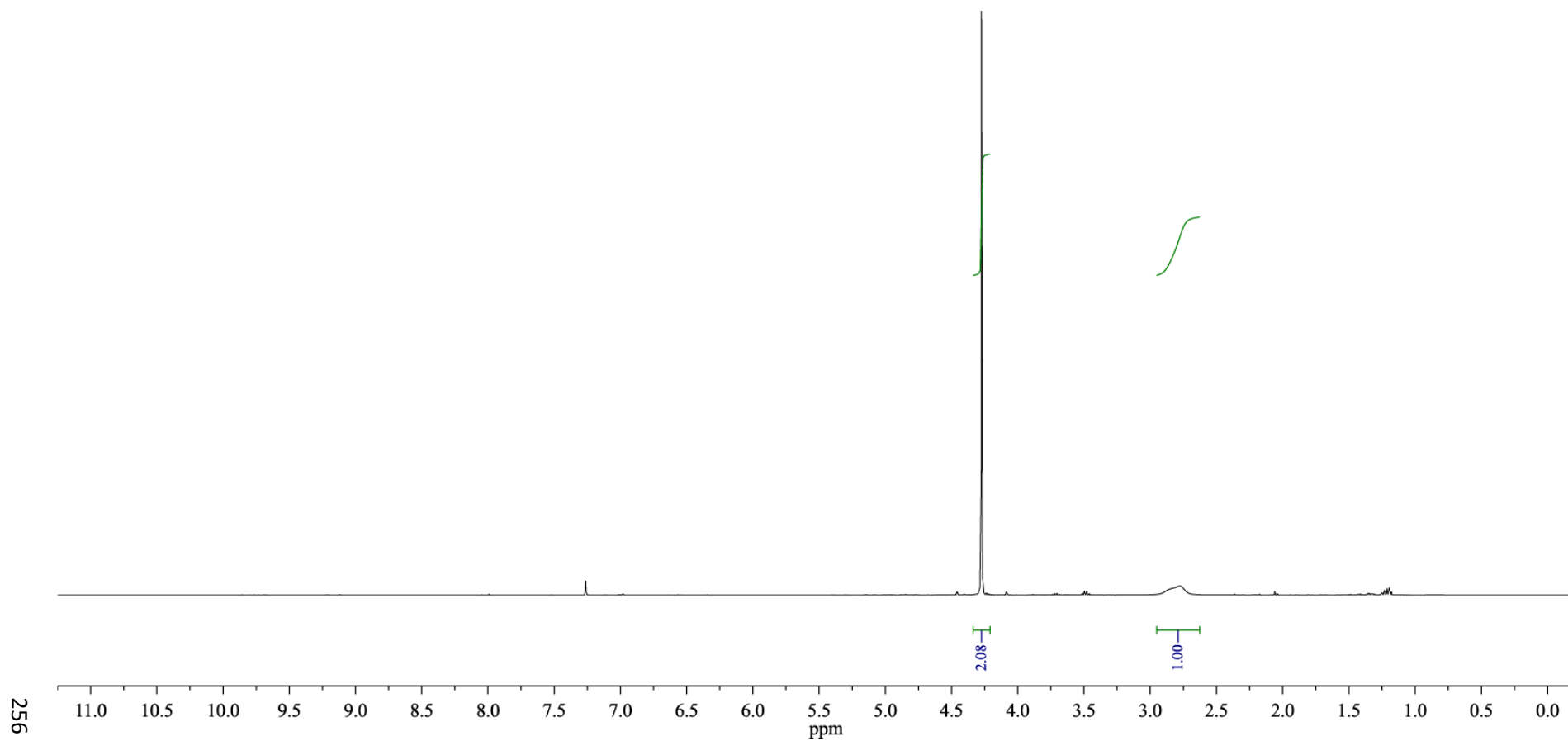
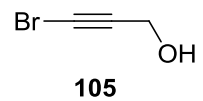
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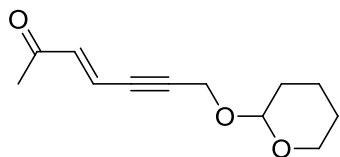




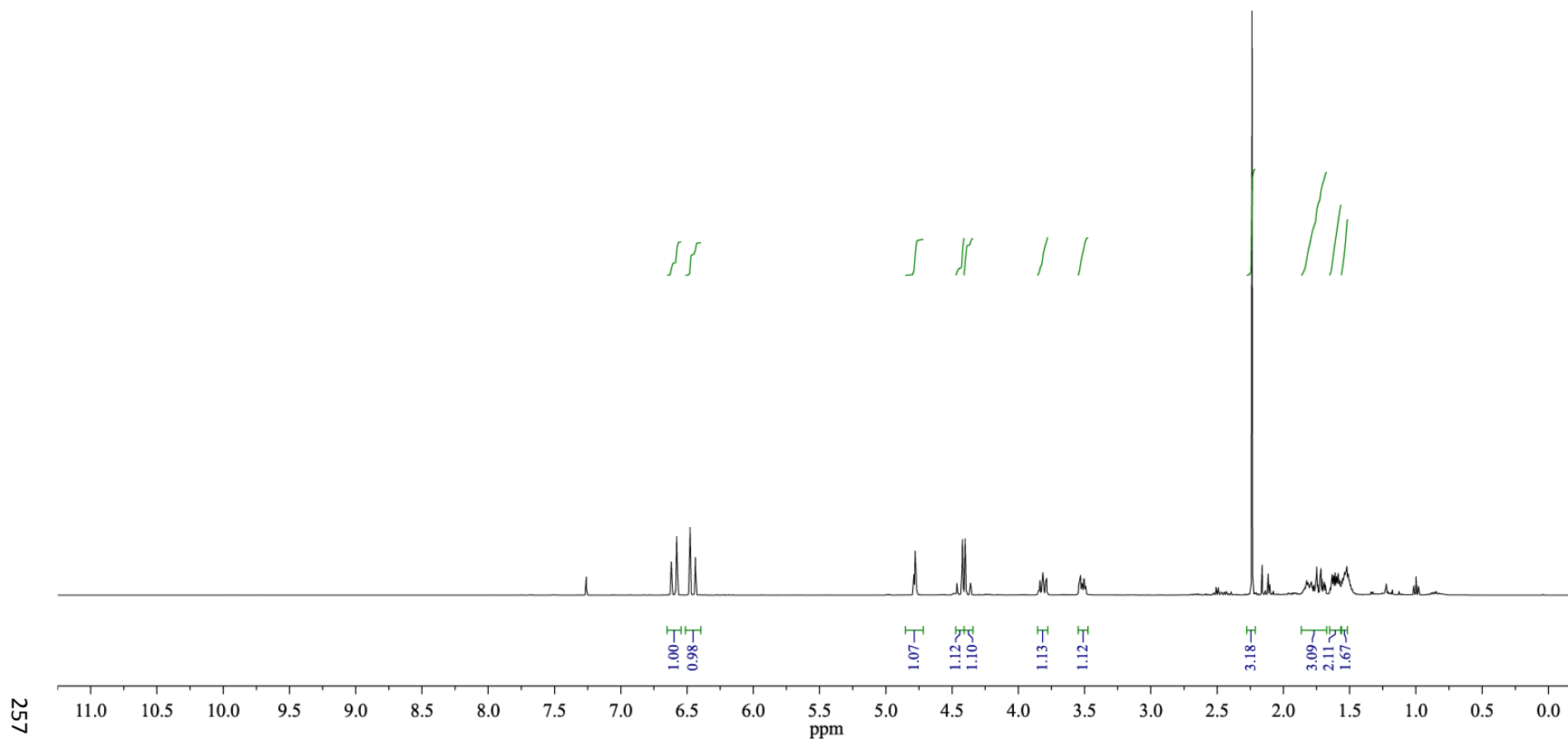


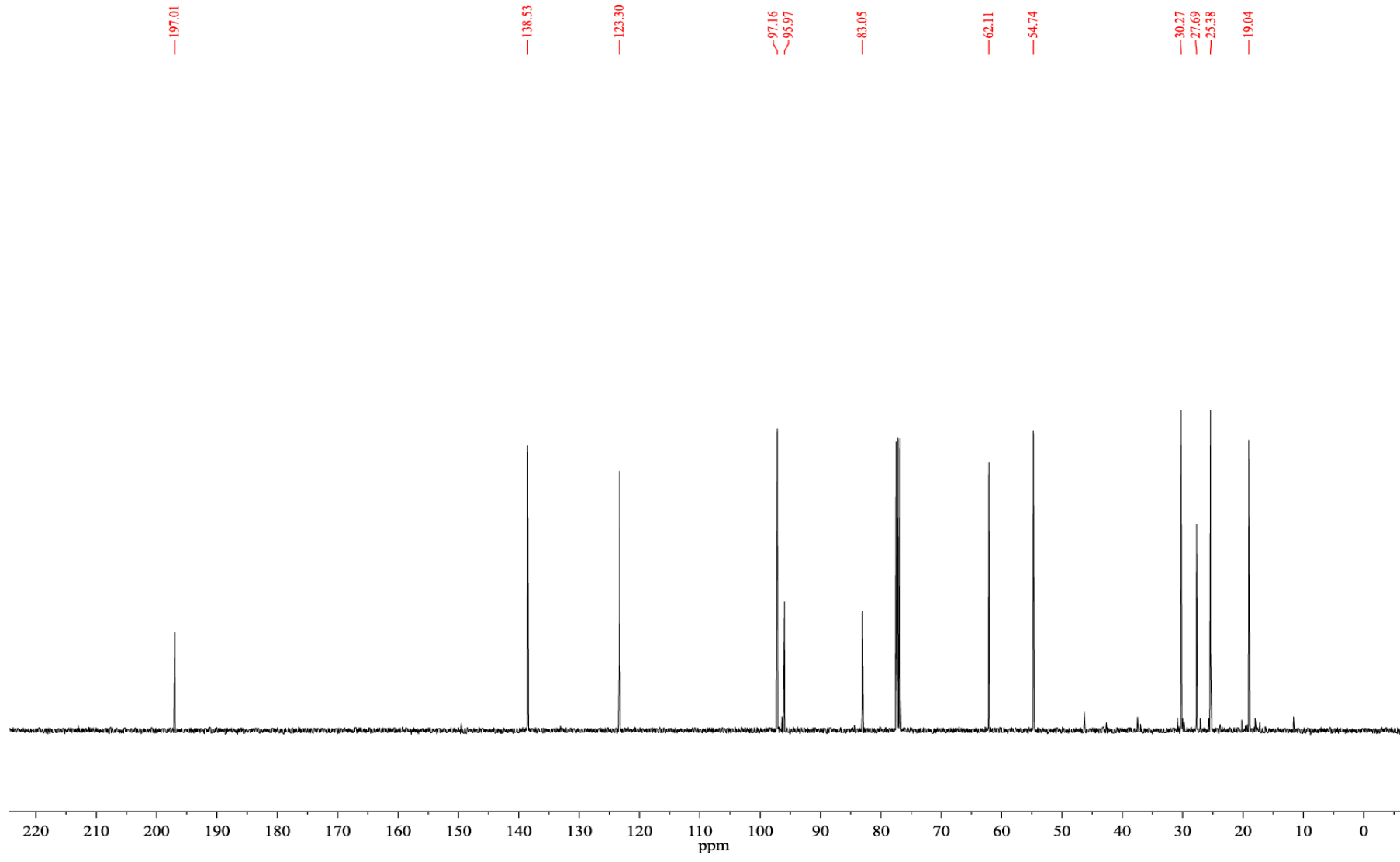


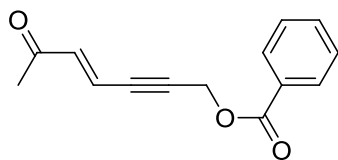




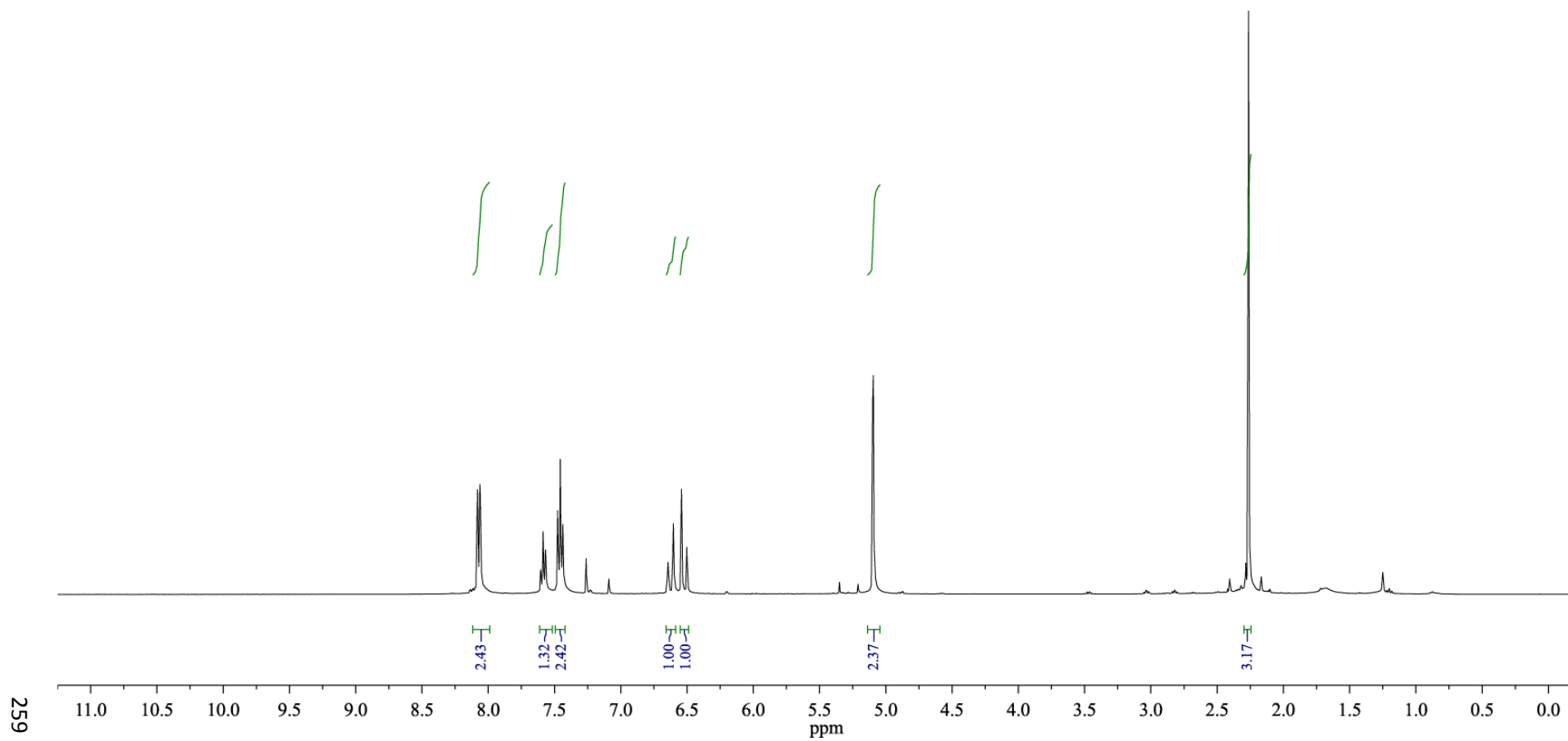
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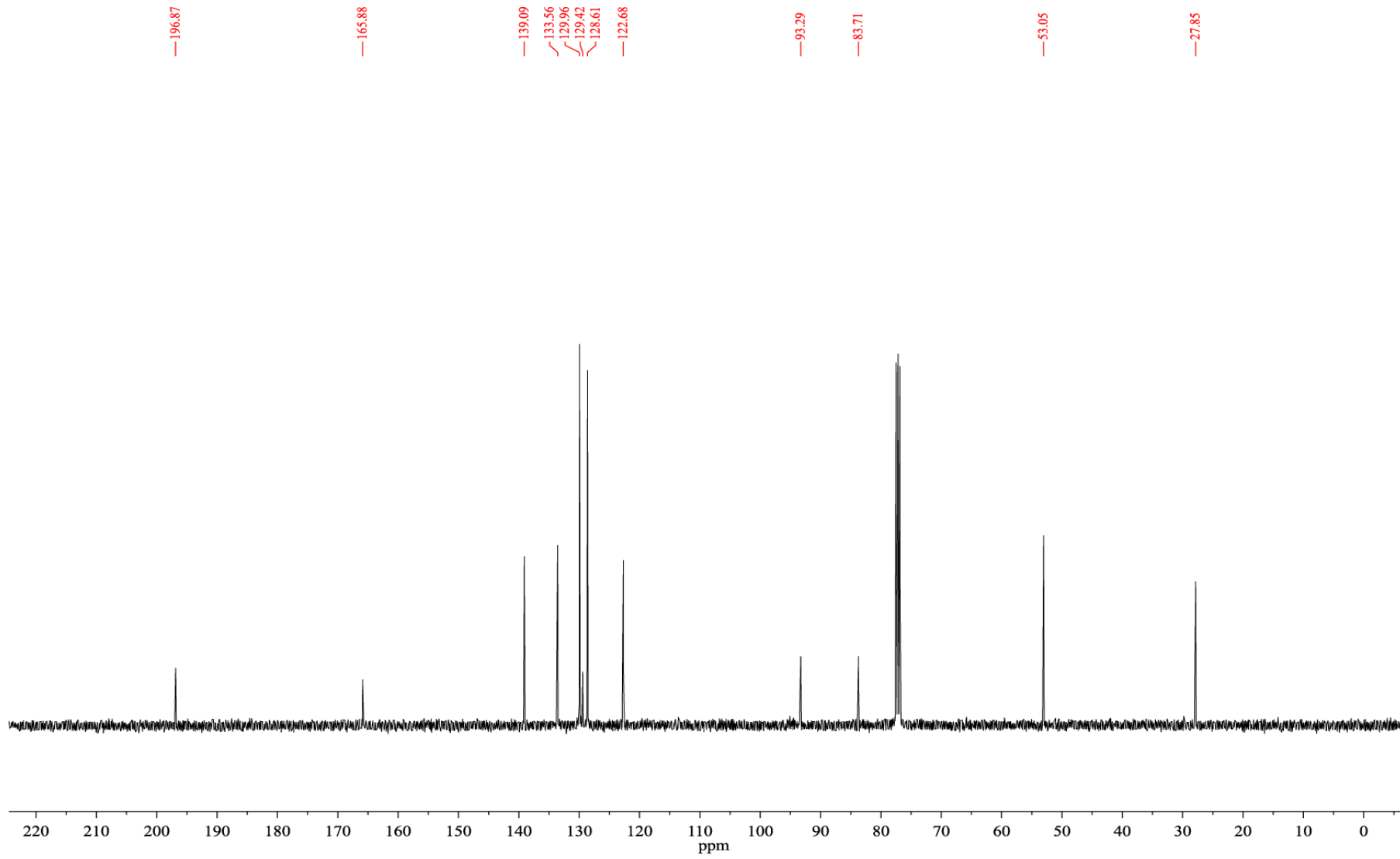


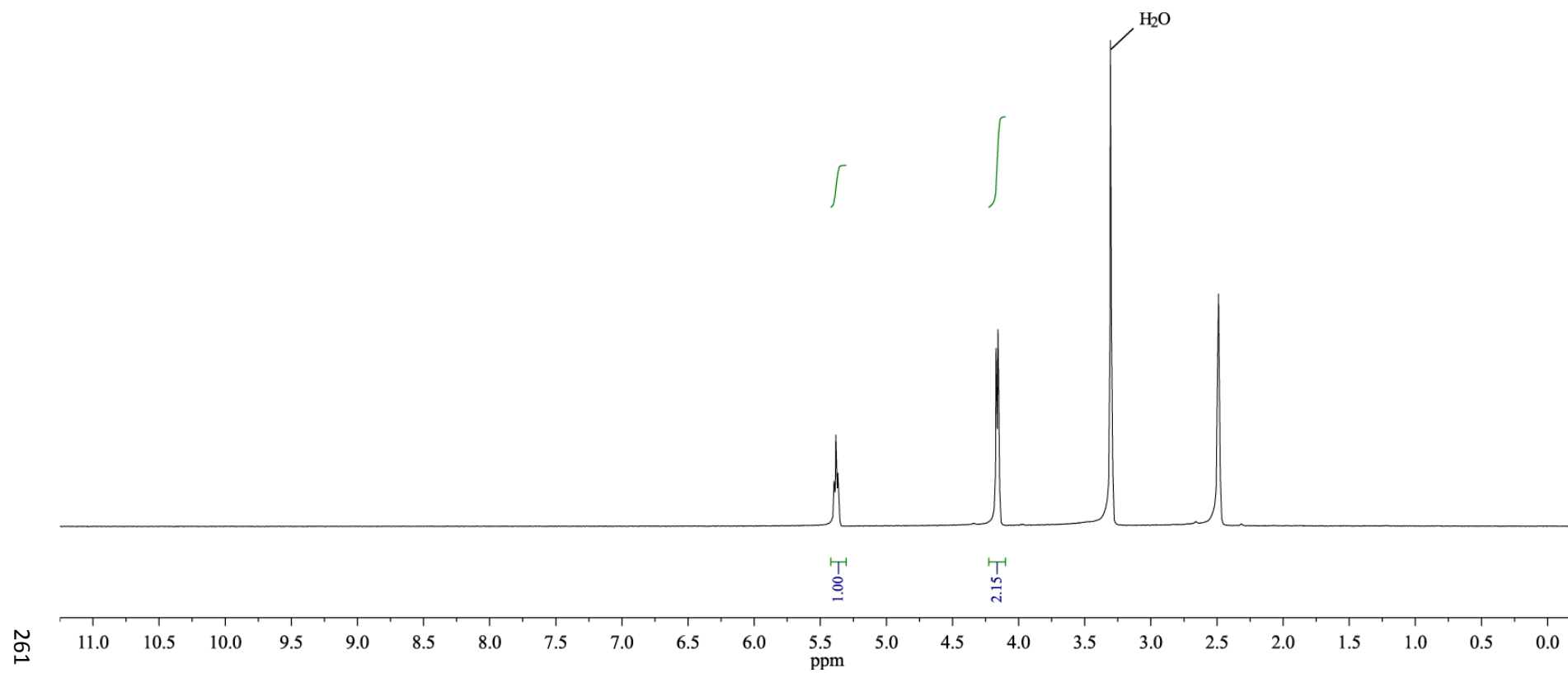
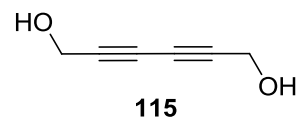


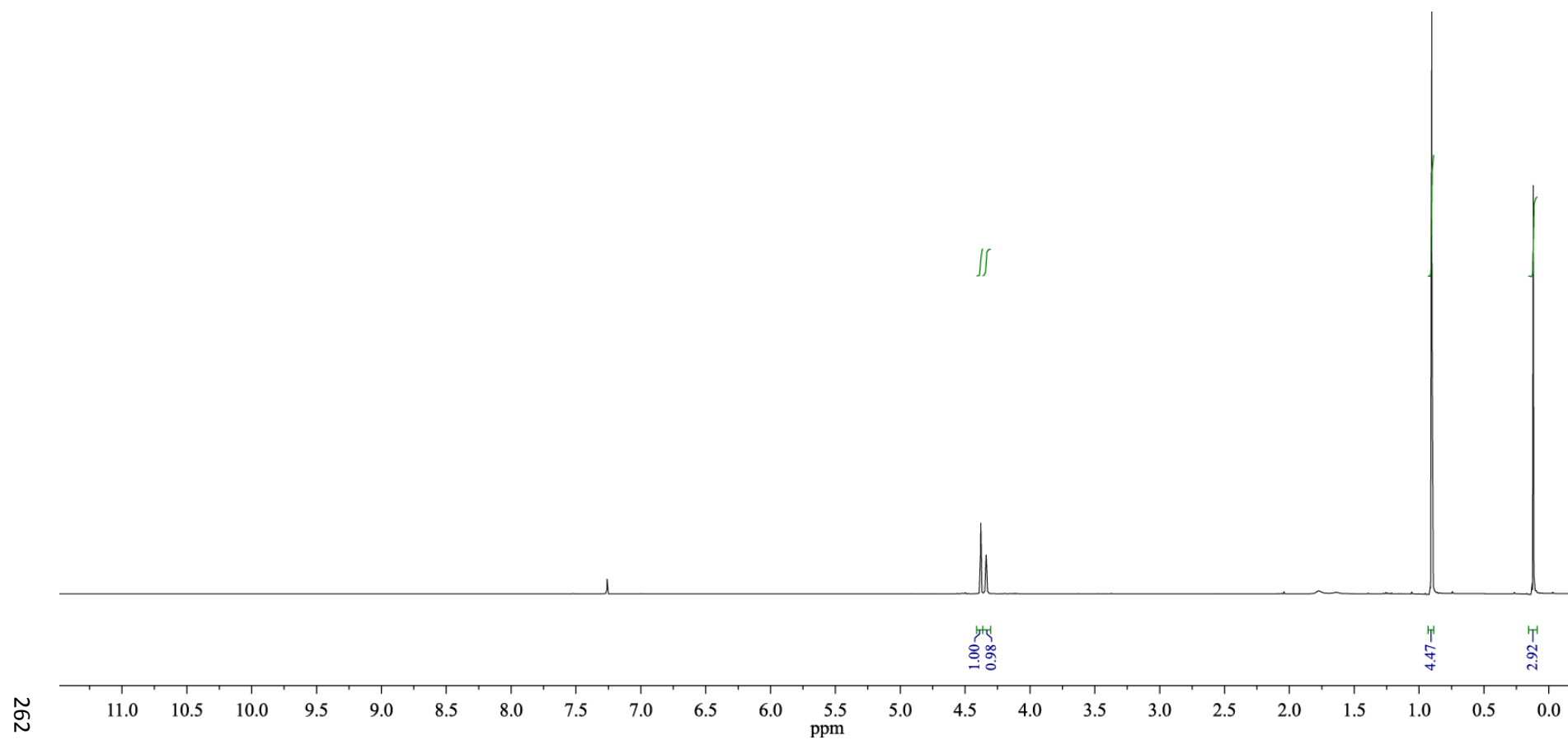
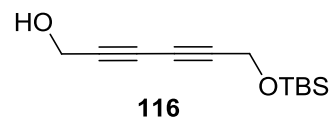


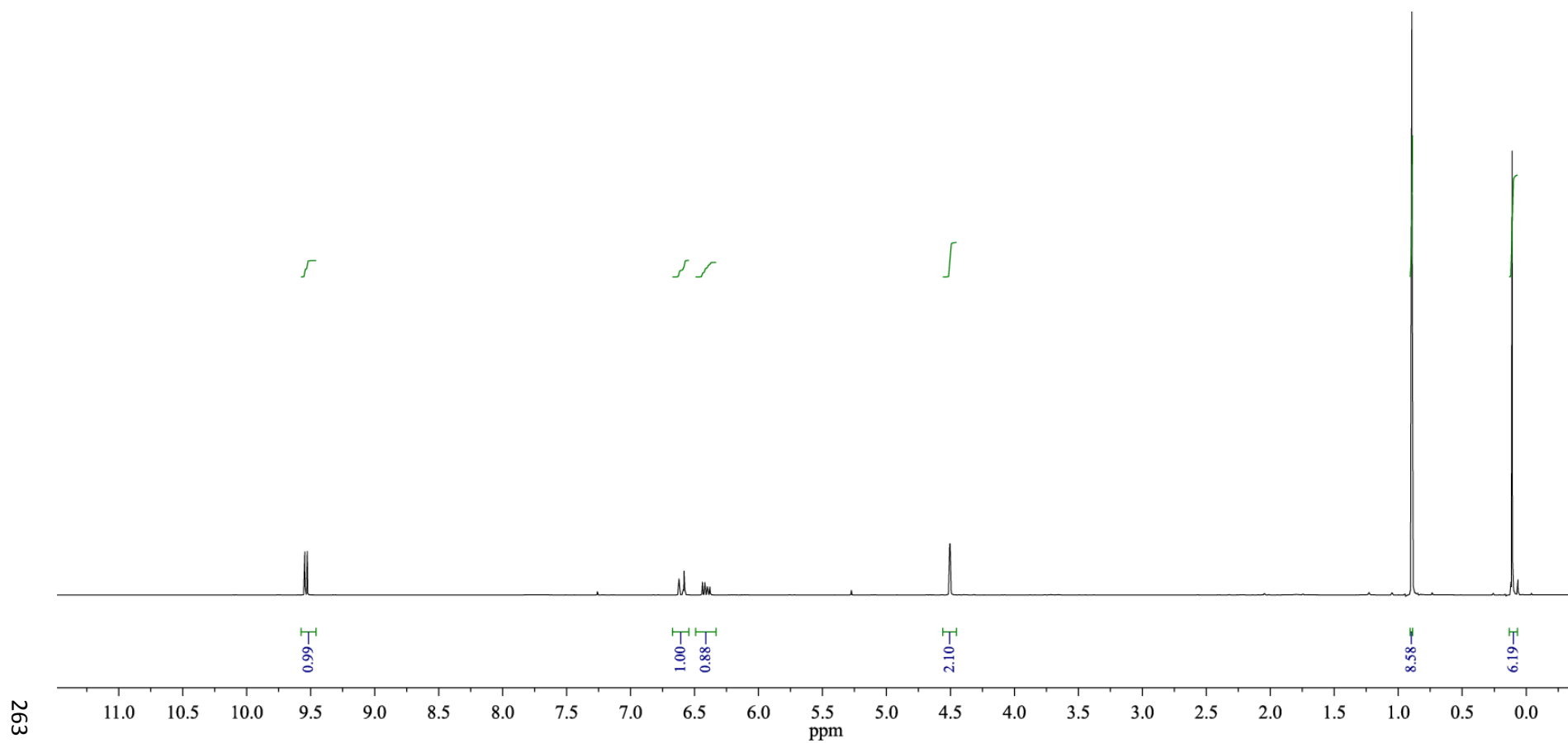
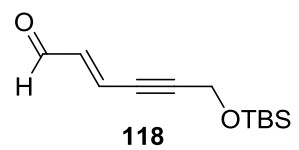
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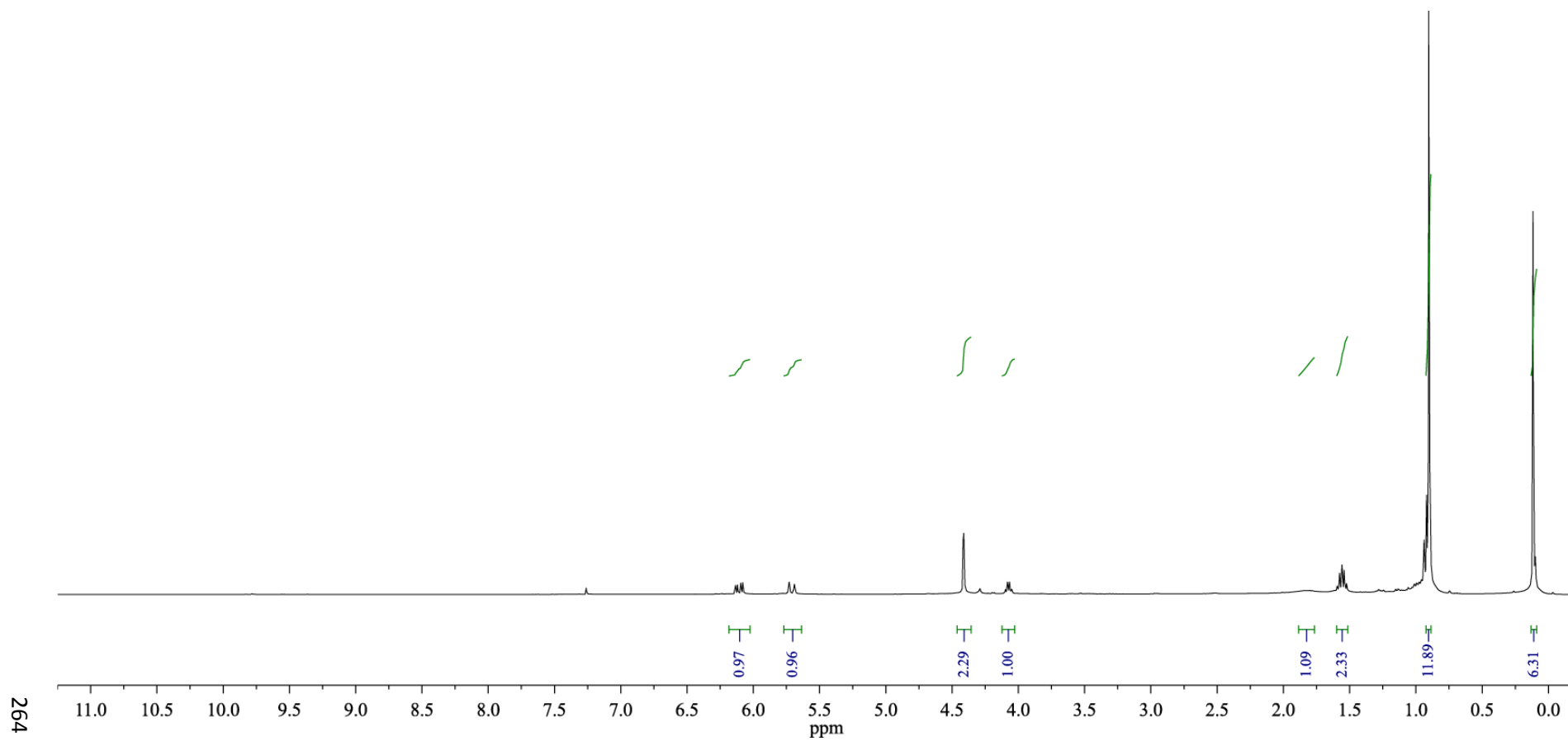
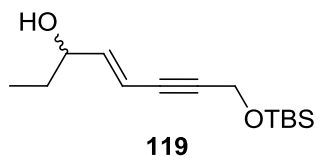


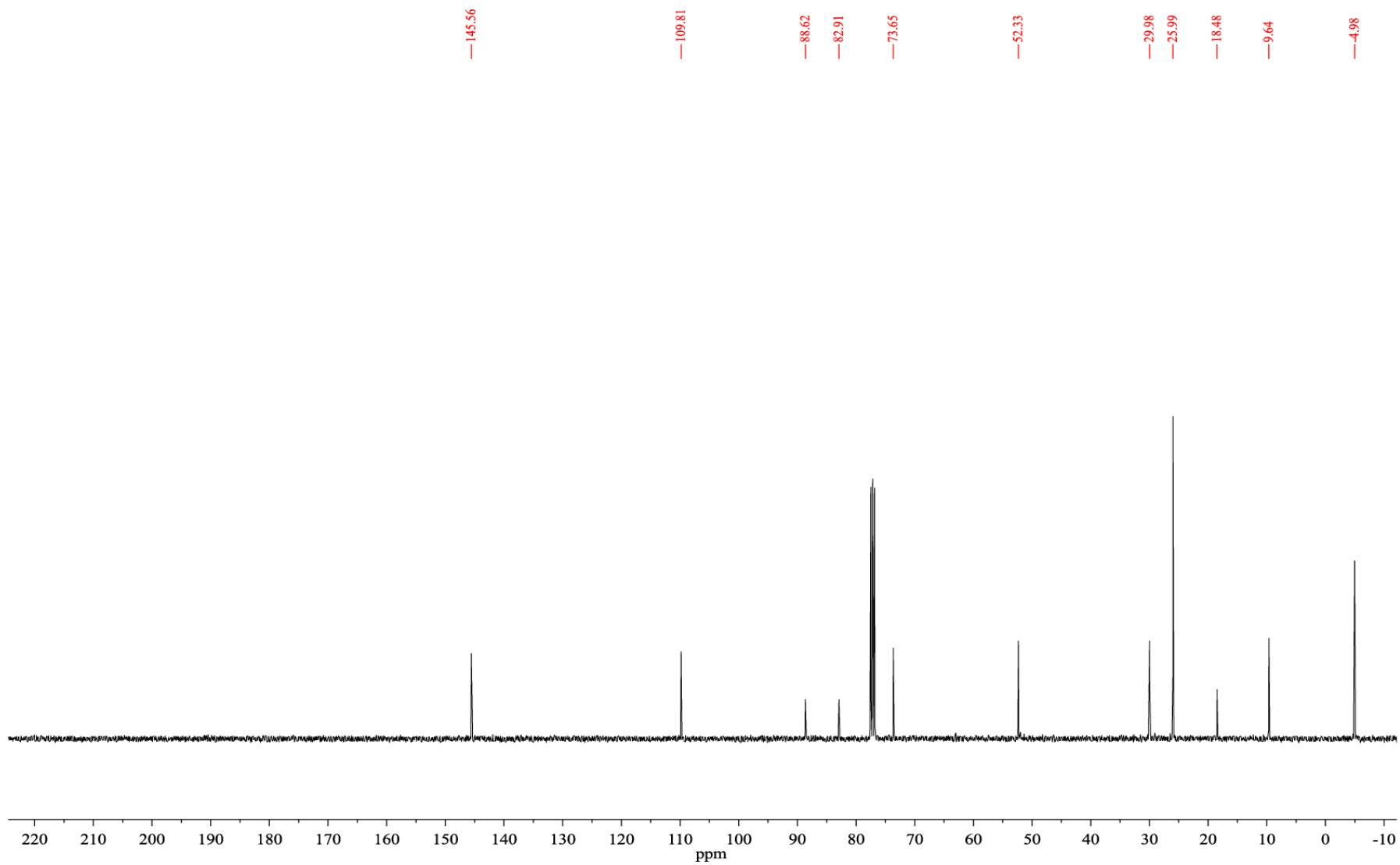


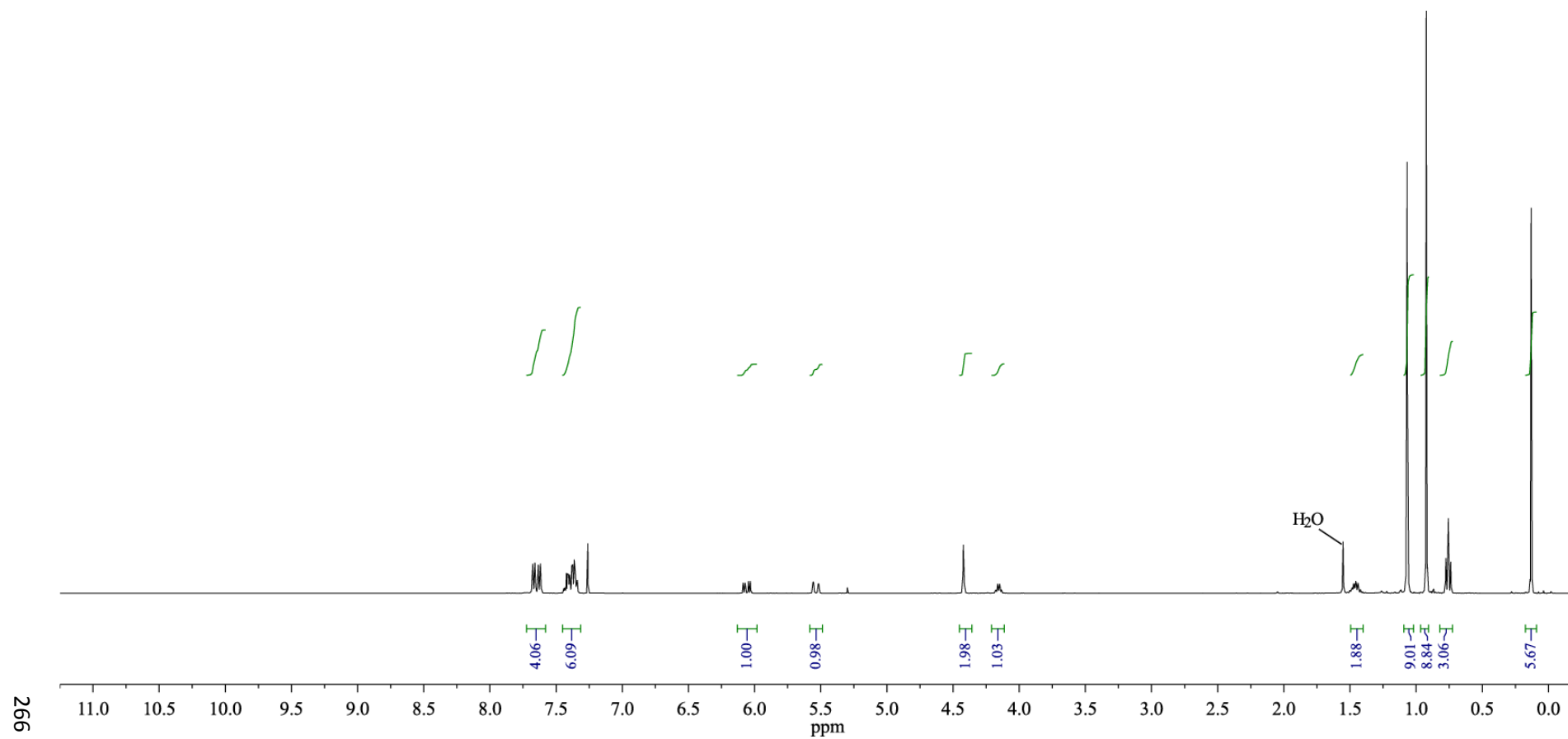
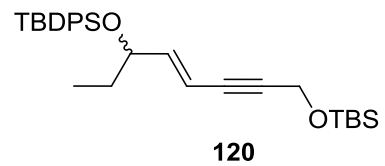


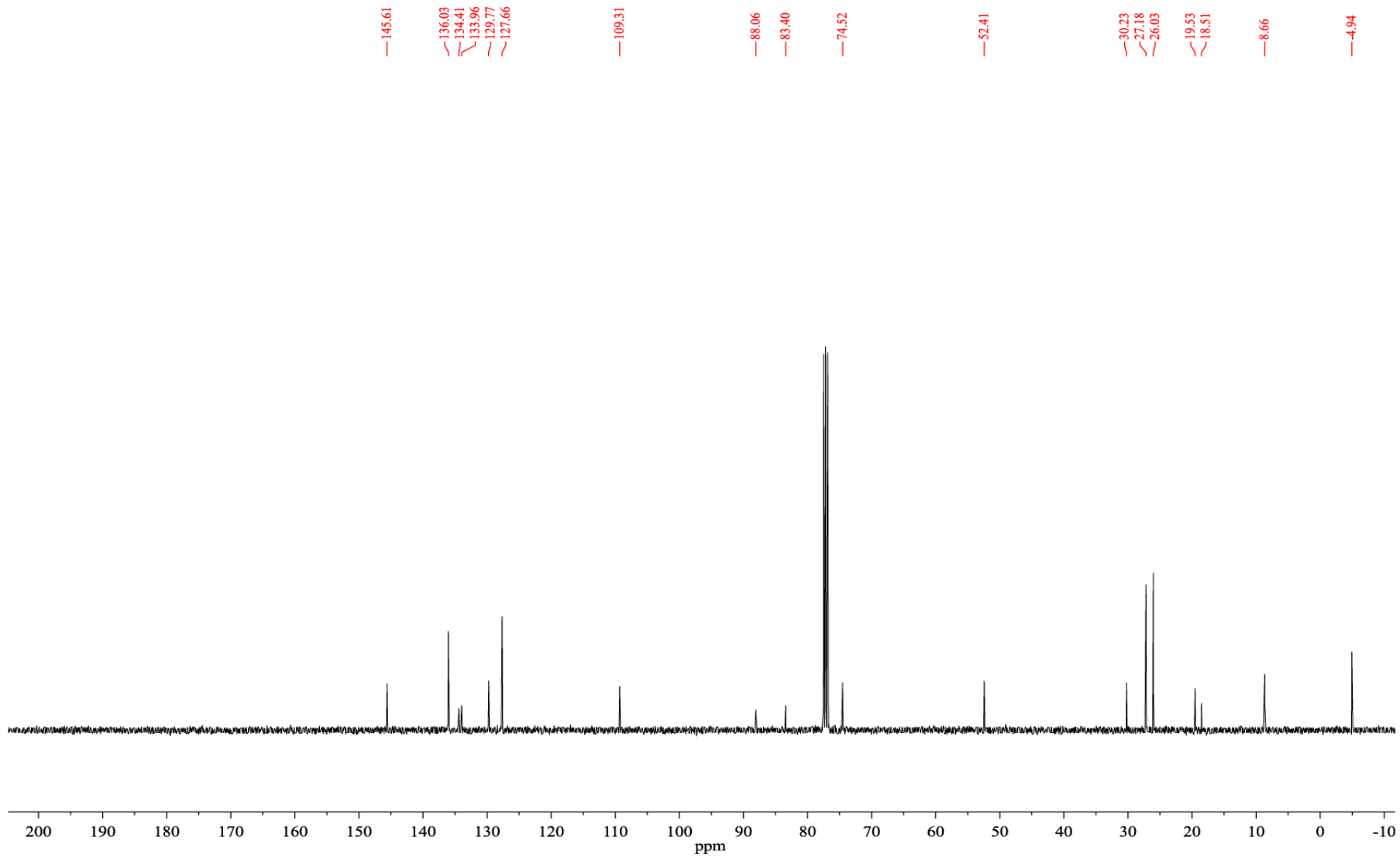




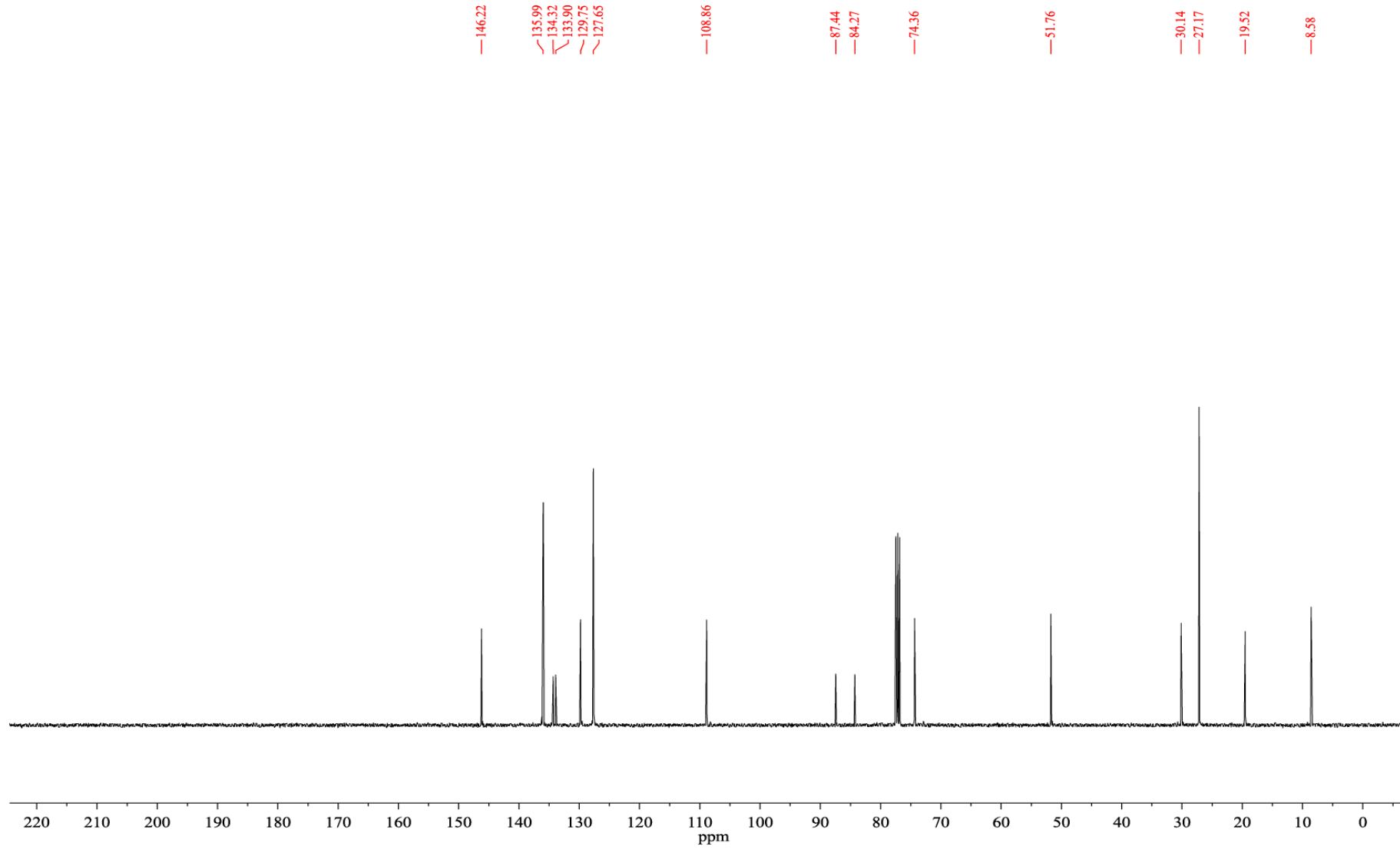


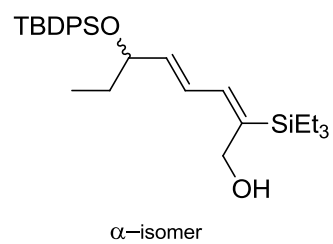




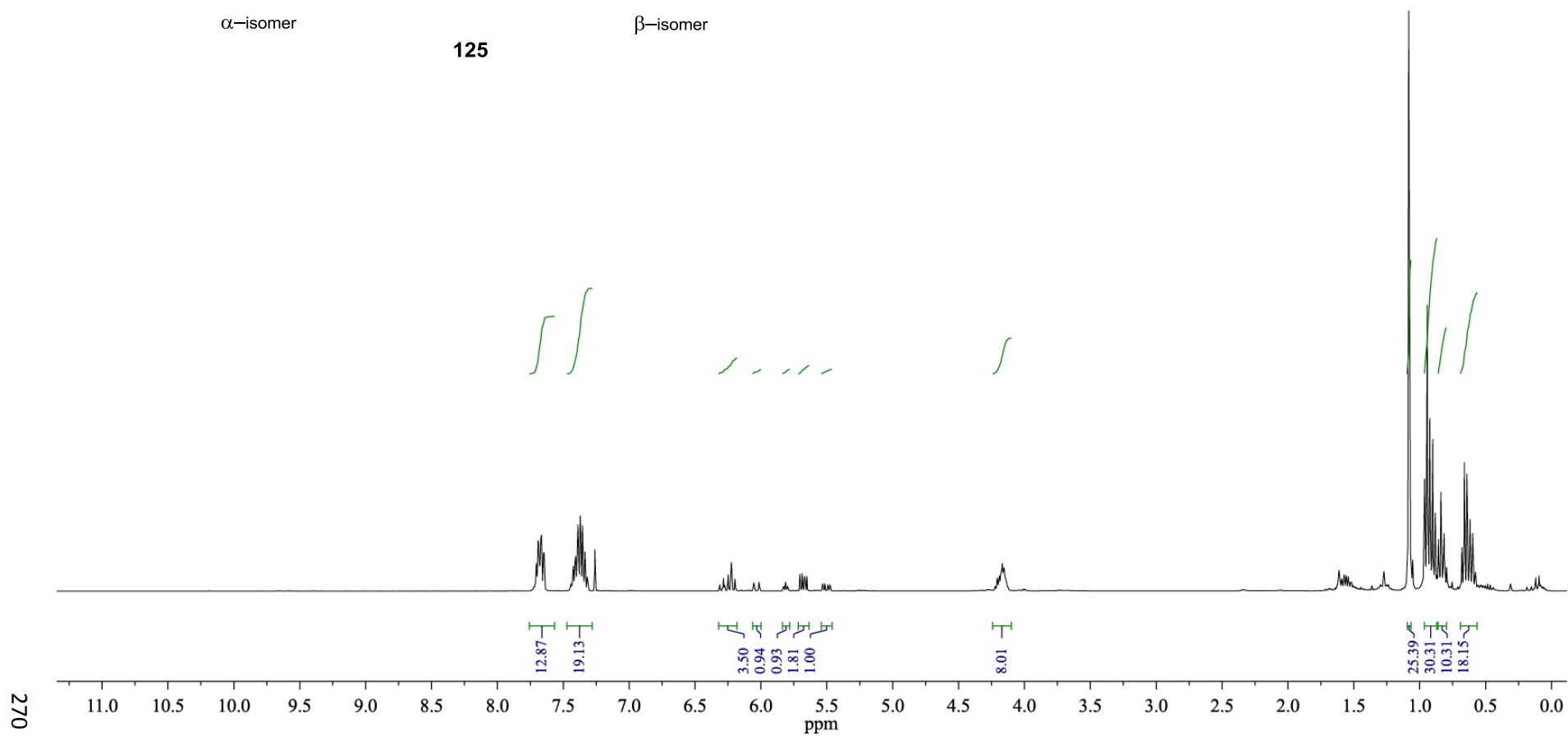
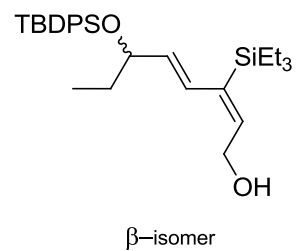


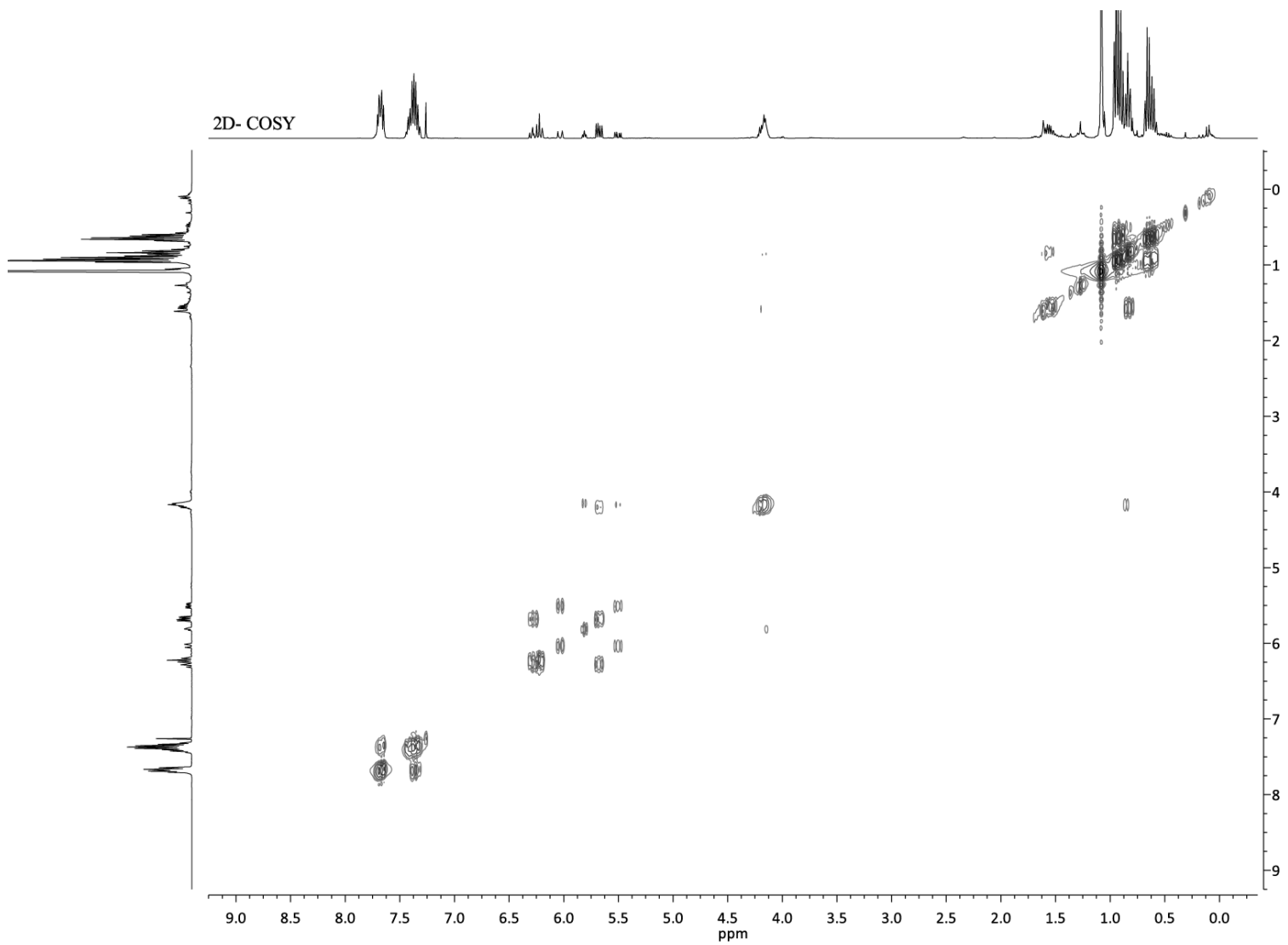


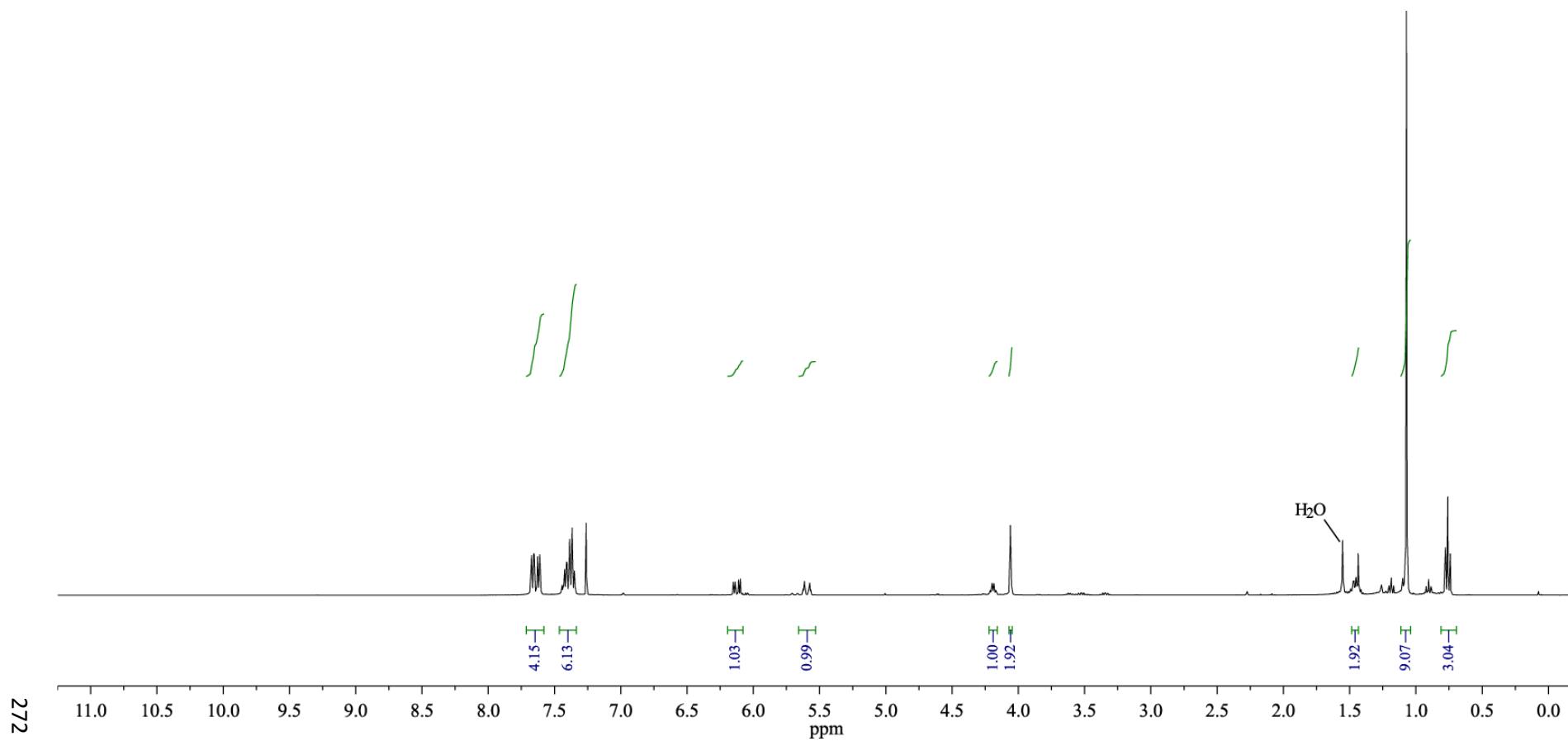
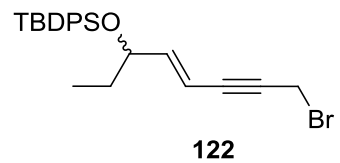


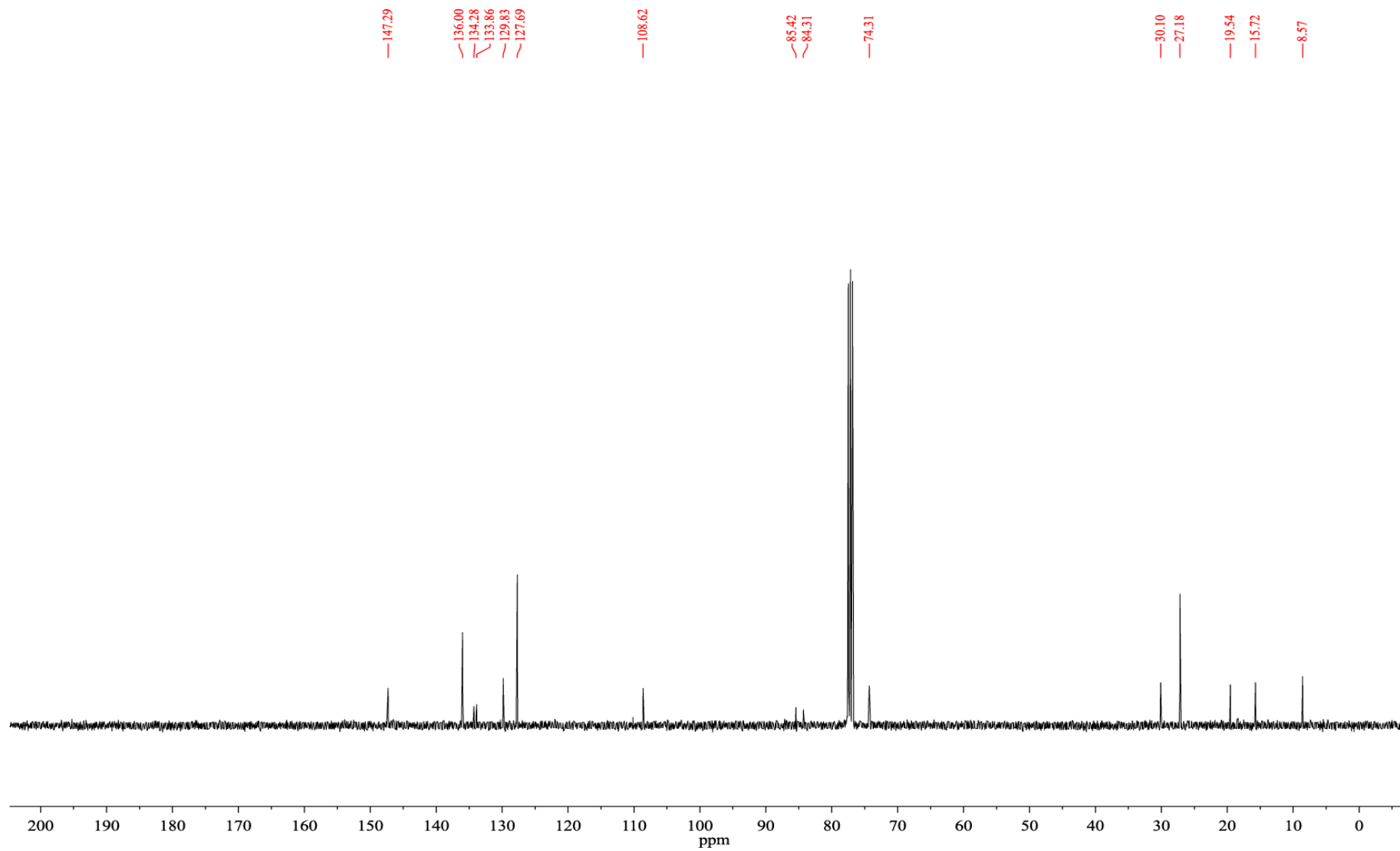


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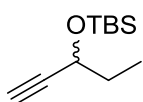




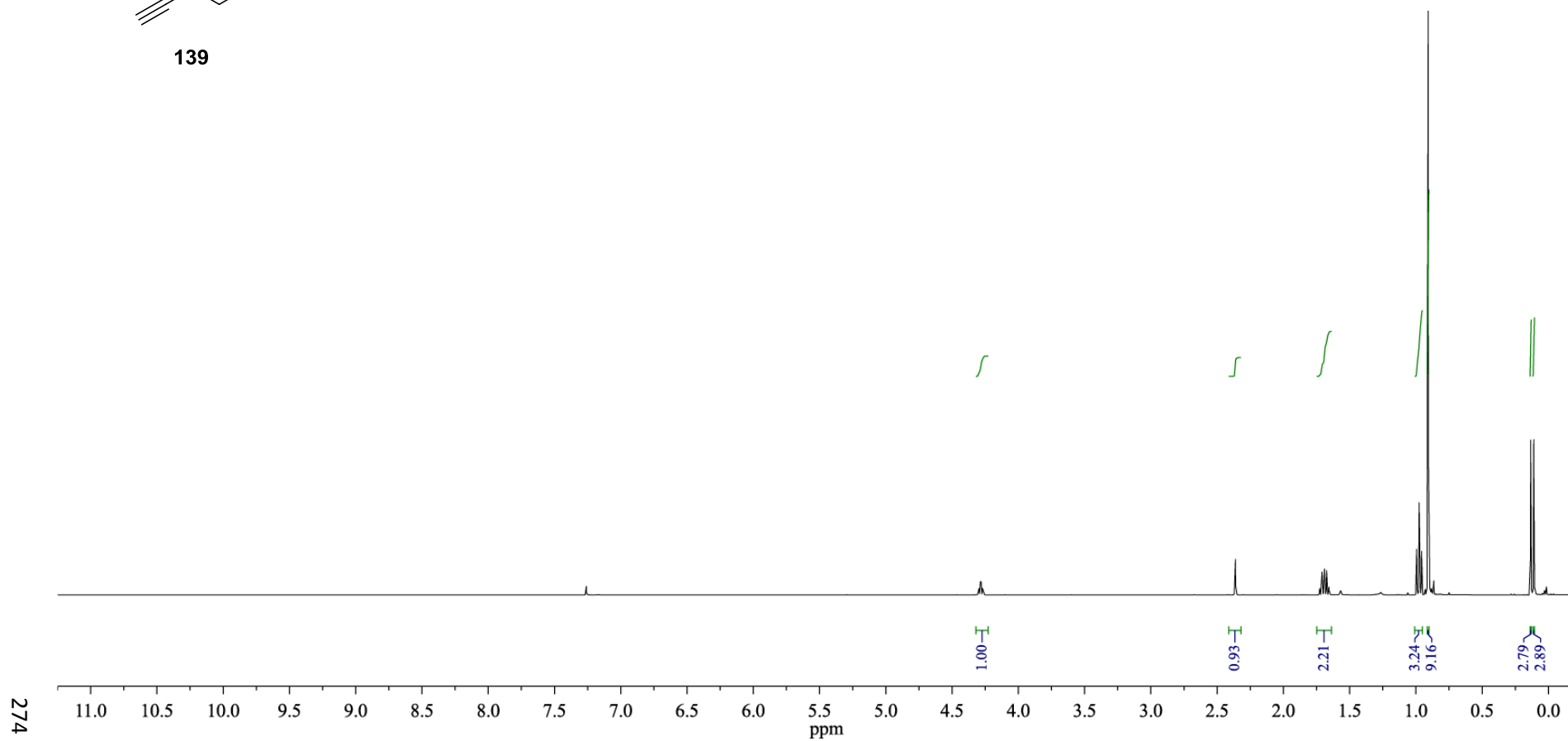


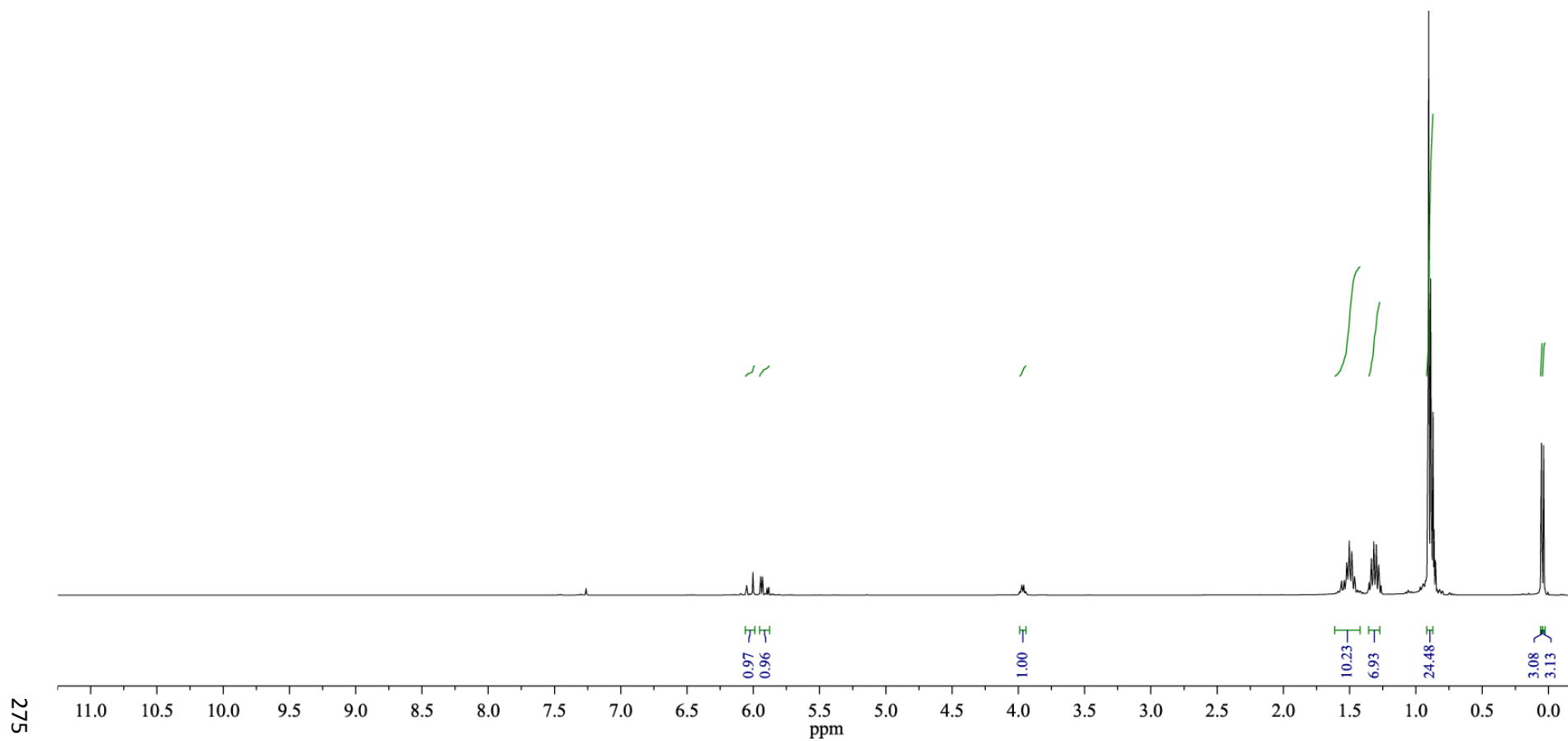
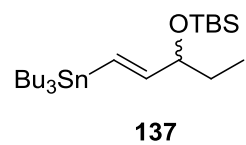


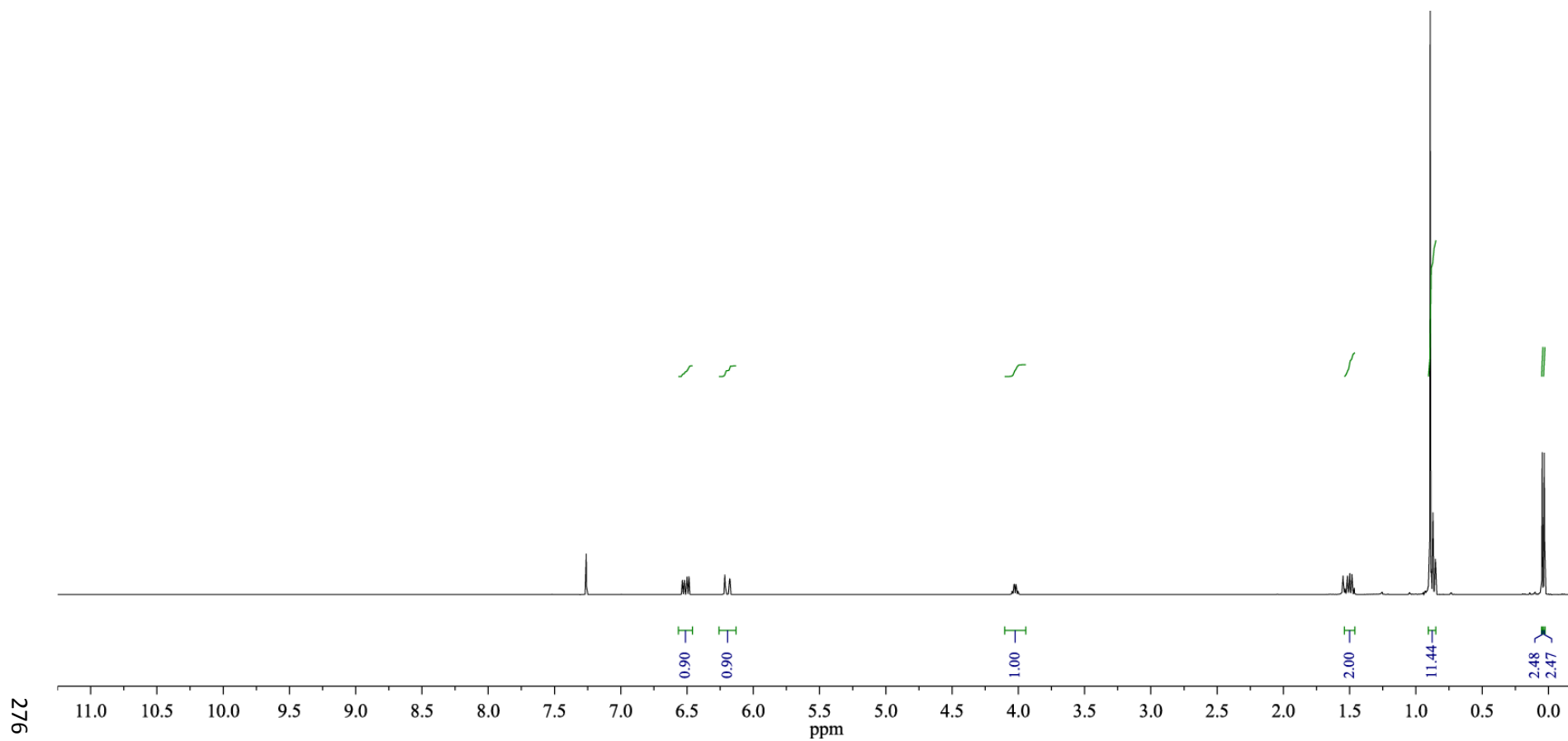
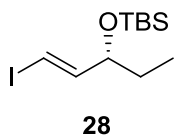
Chapter 3 spectra

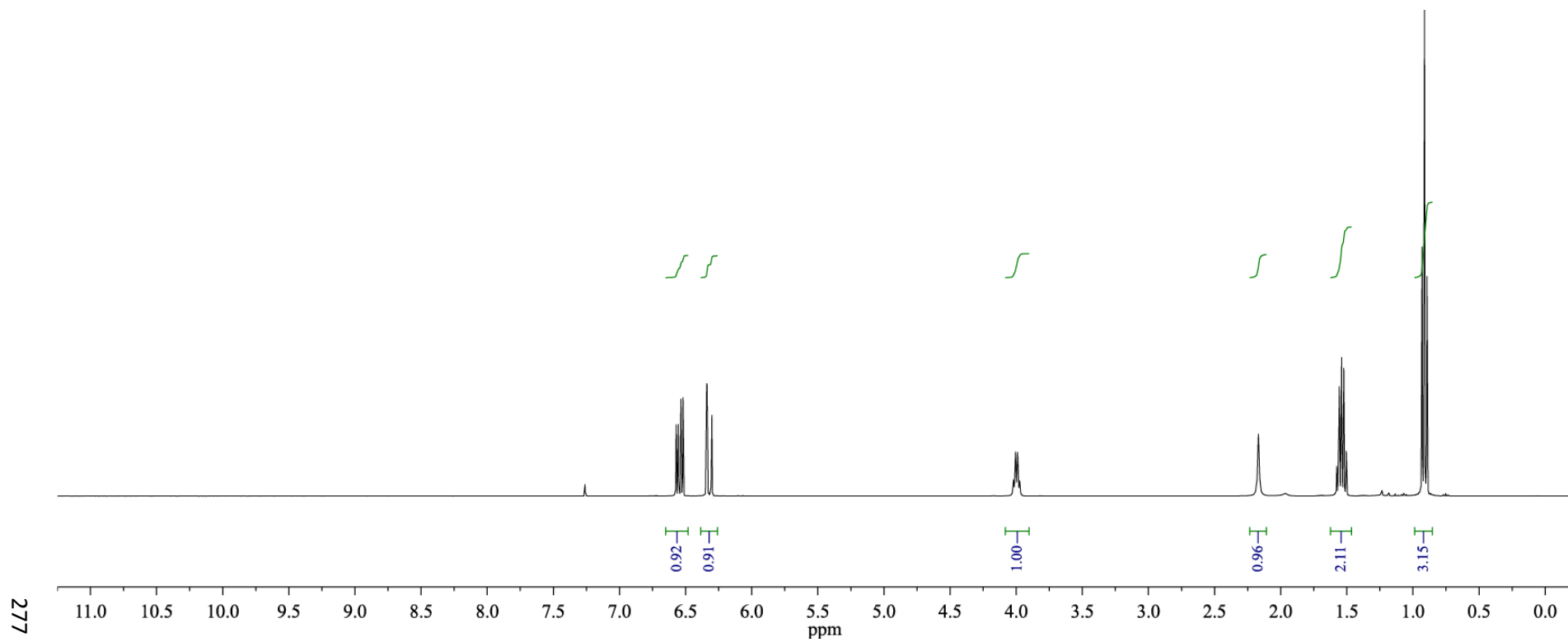
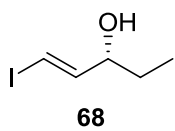


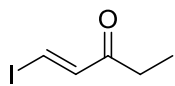
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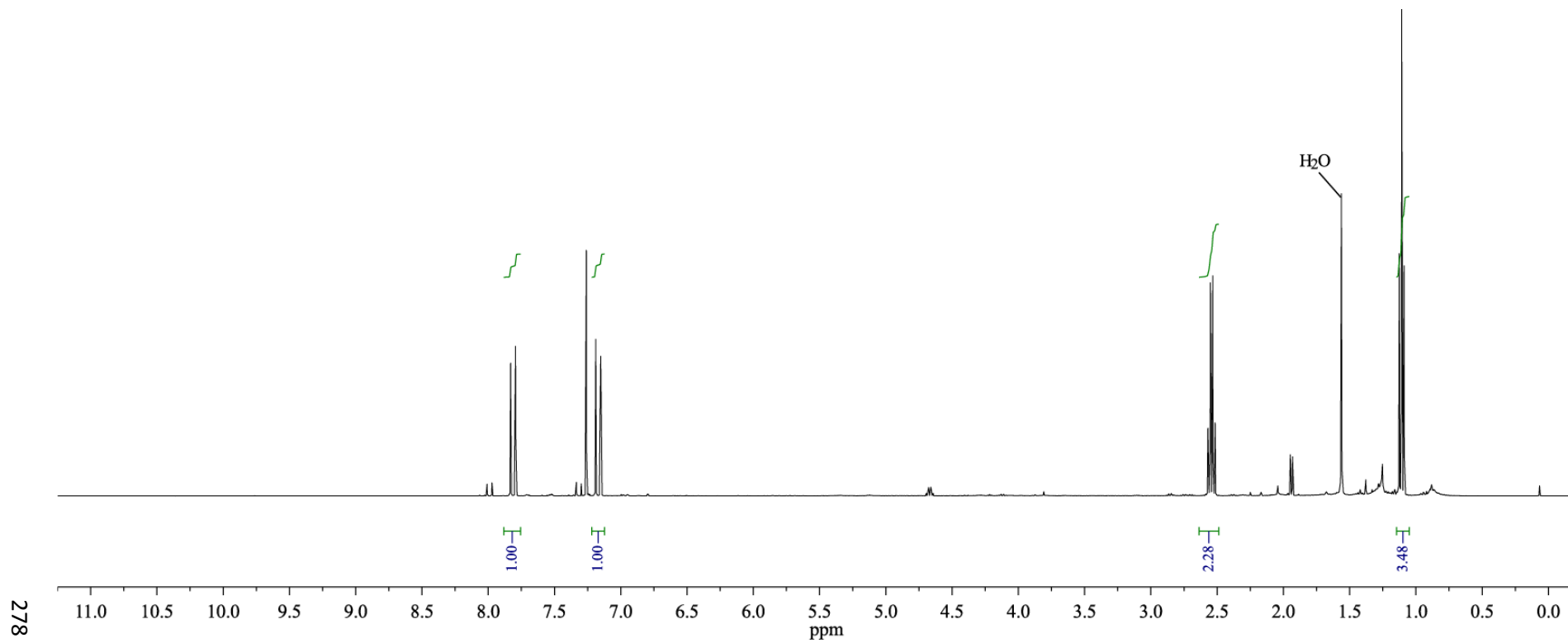


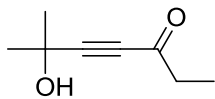




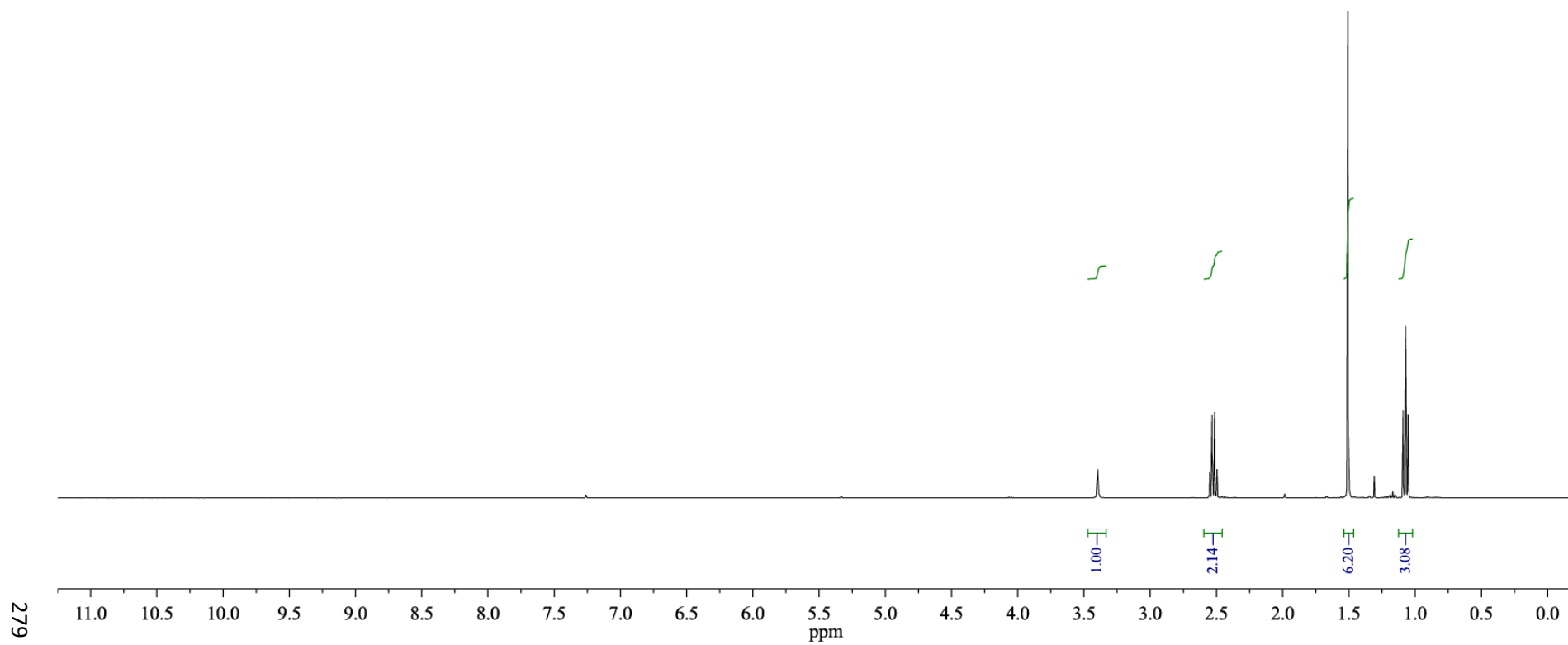


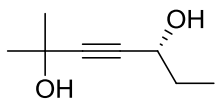
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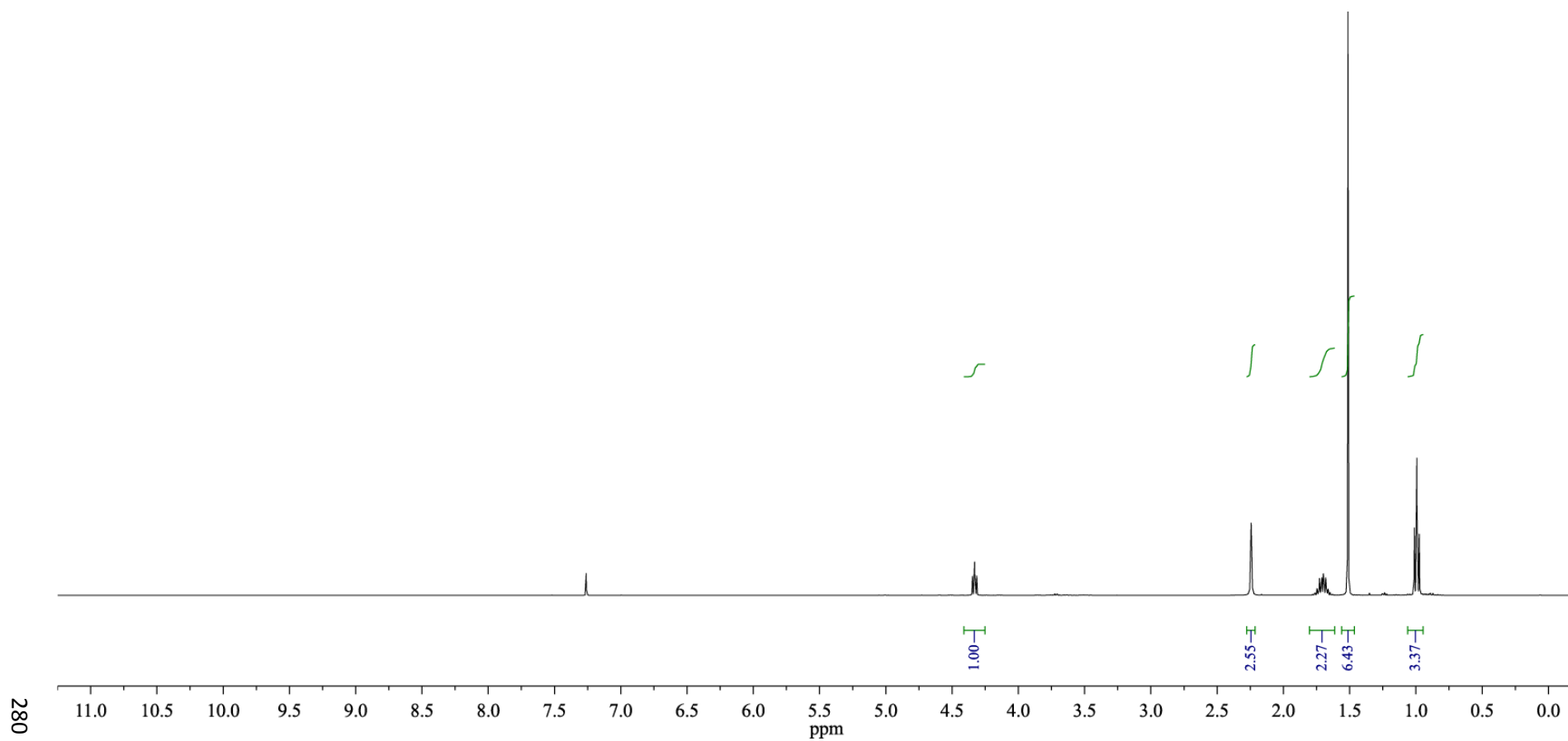


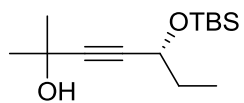
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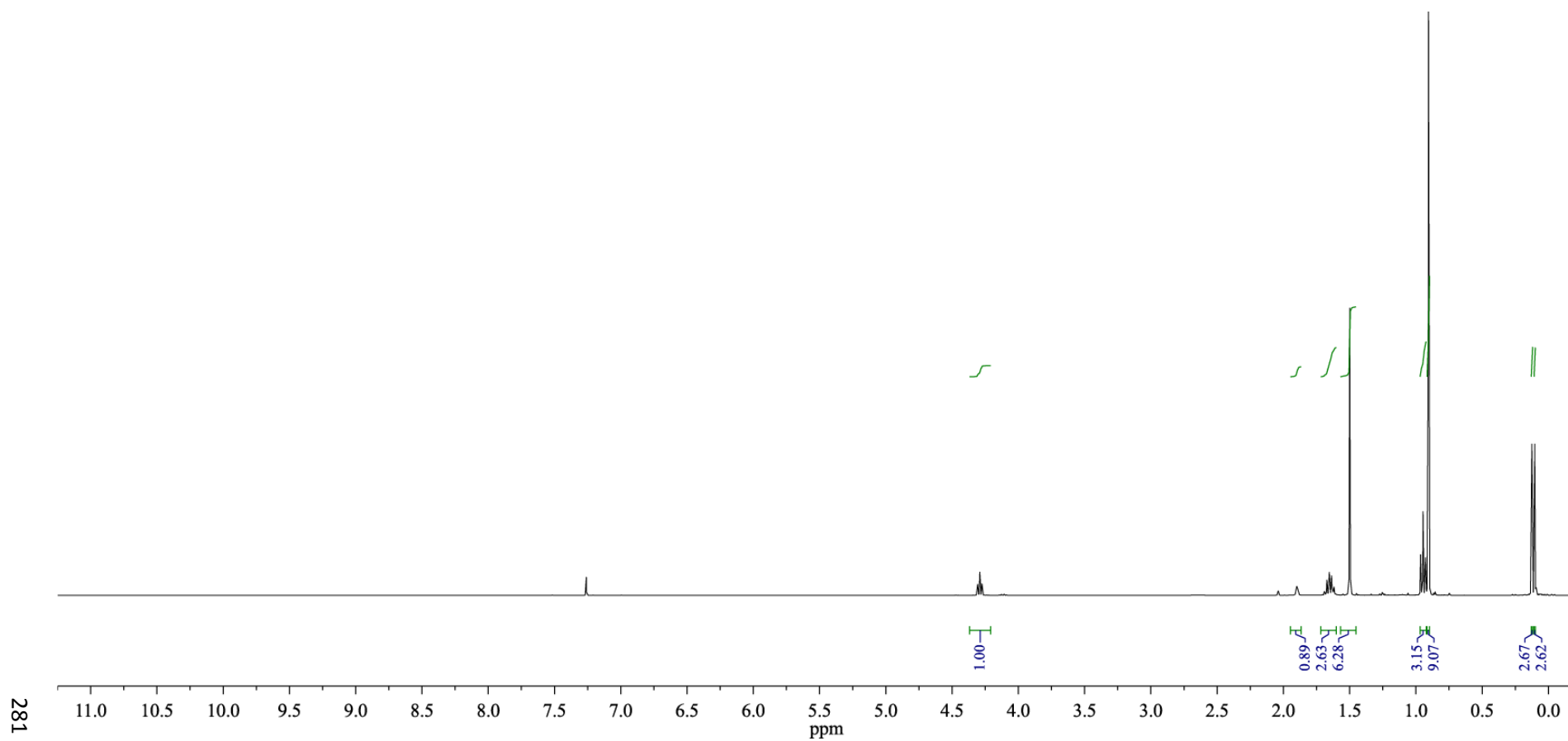


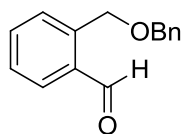
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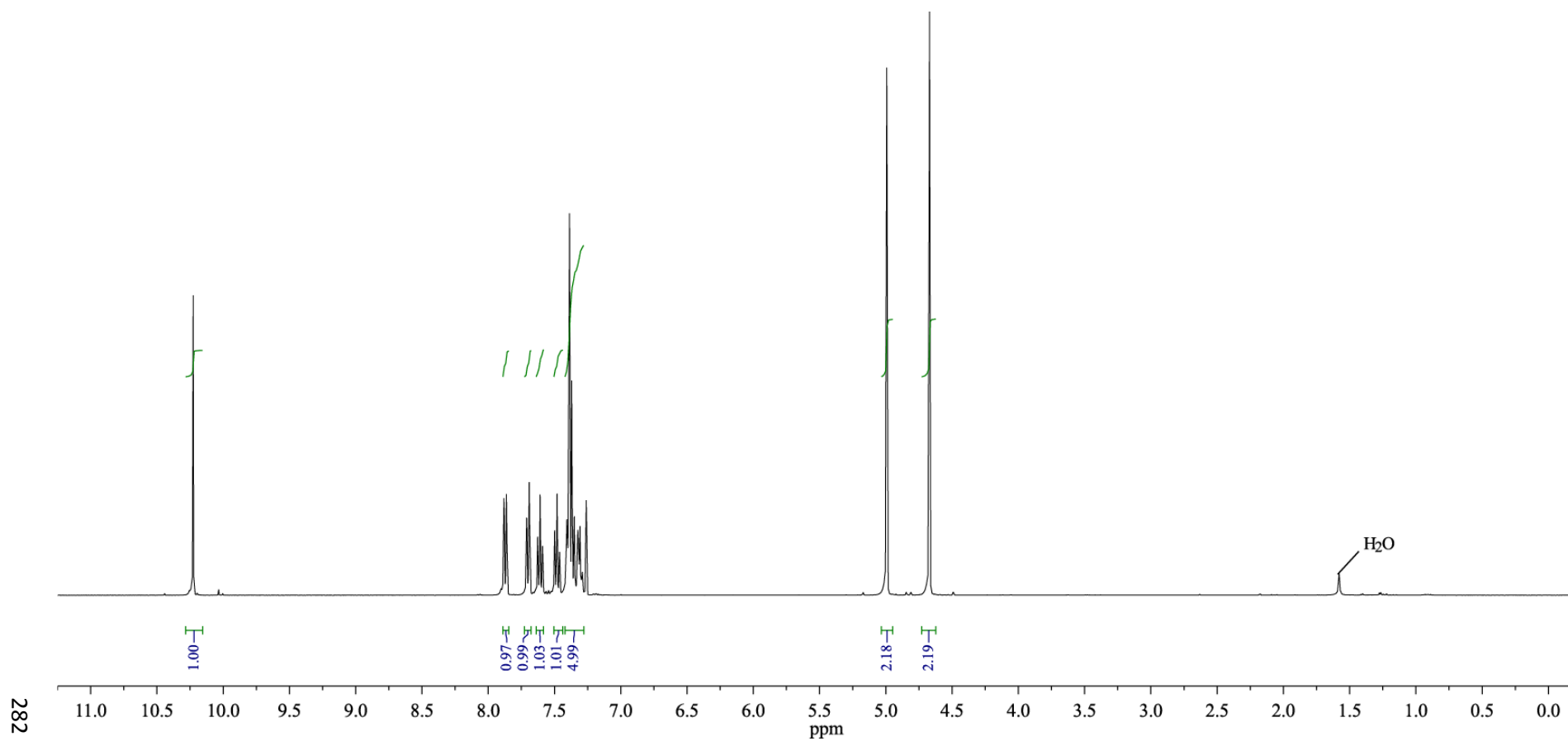


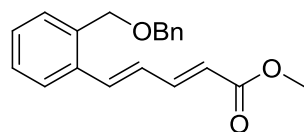
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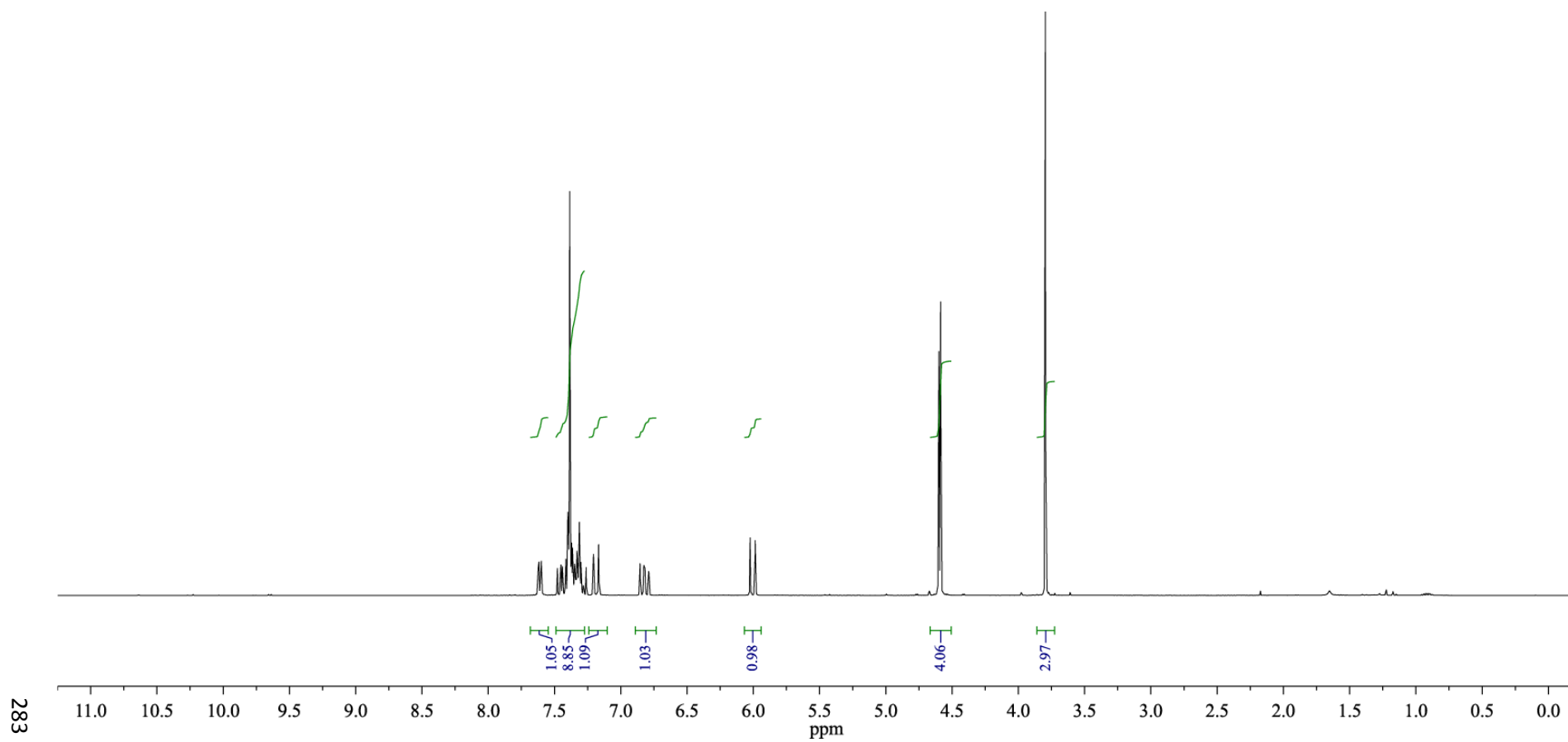


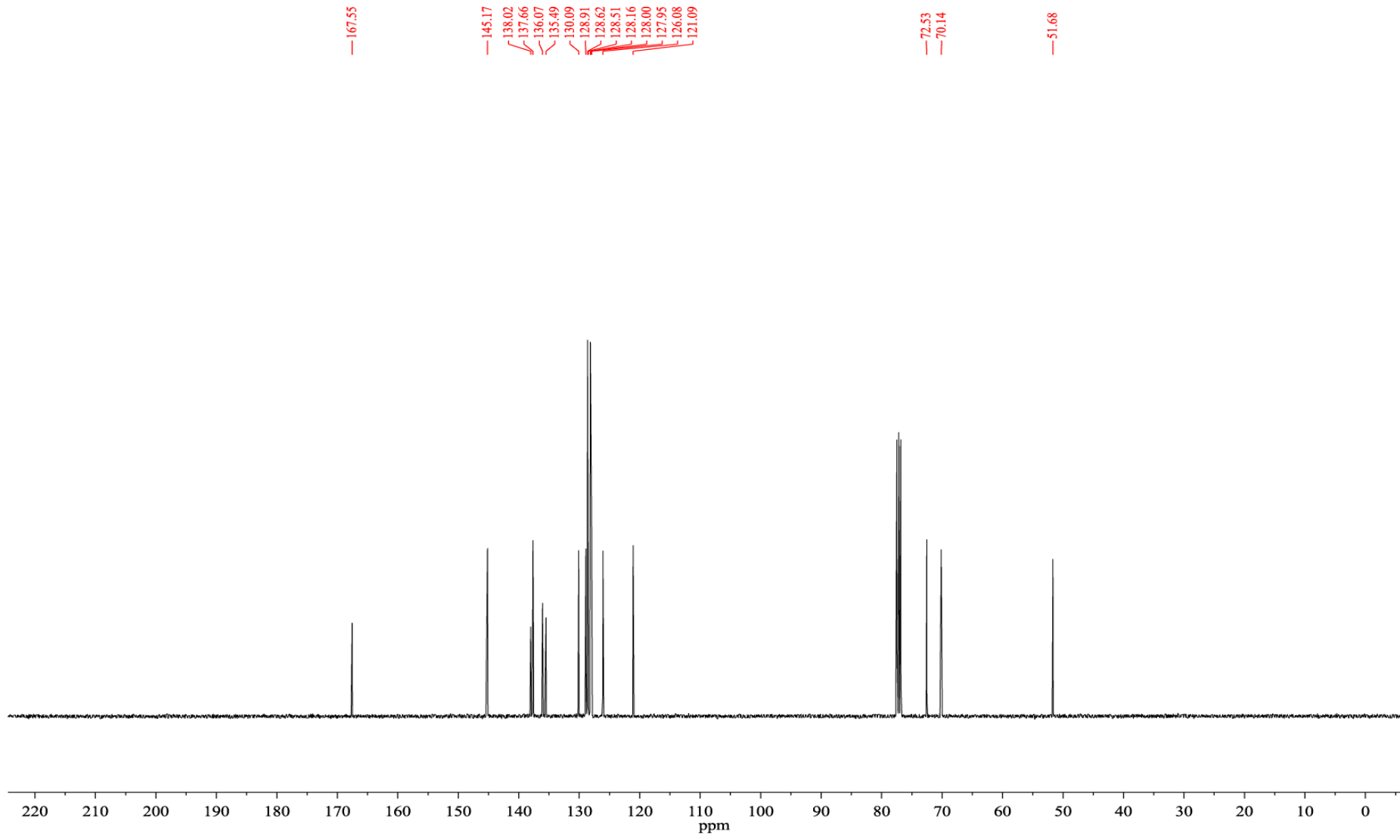
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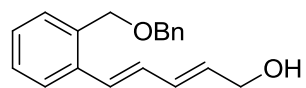




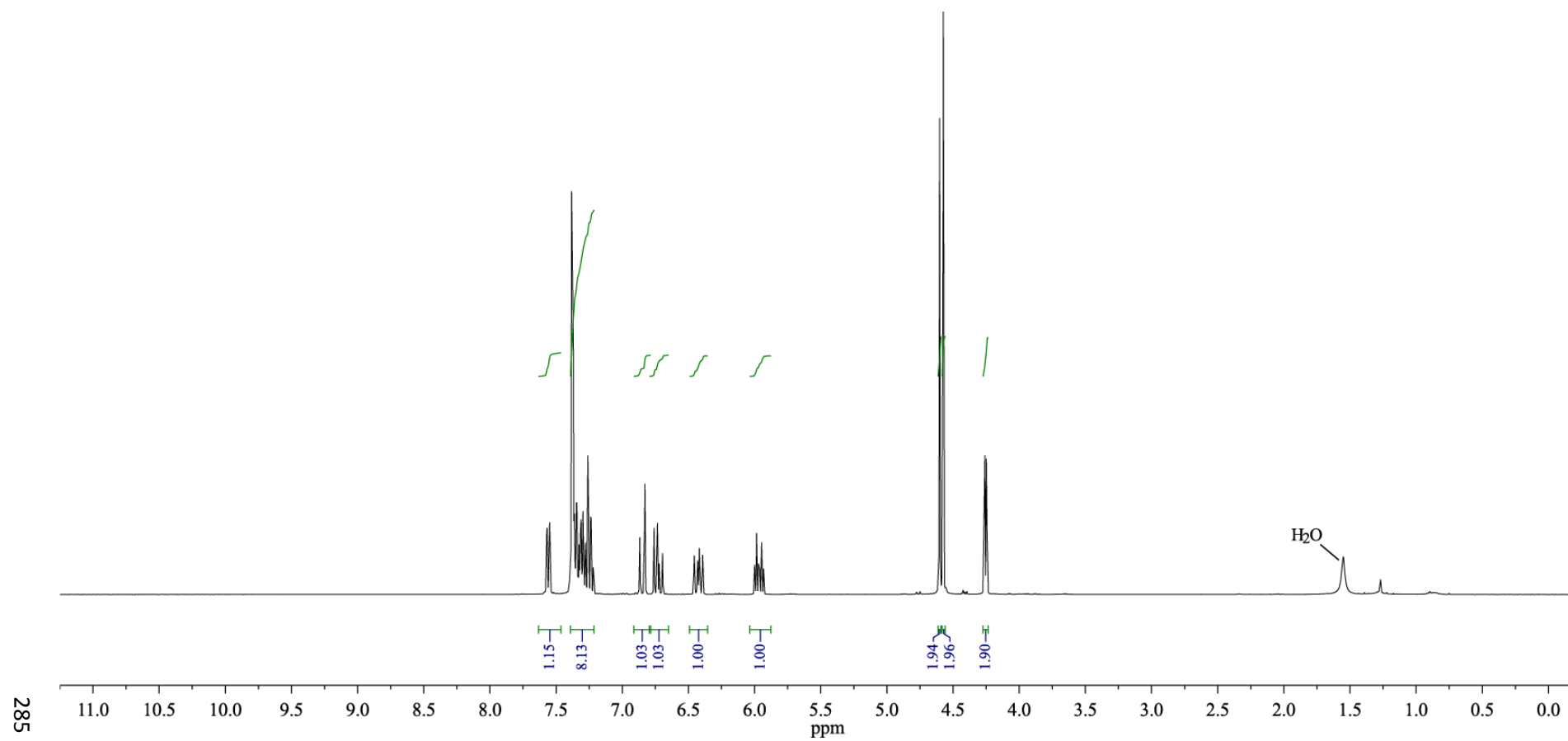
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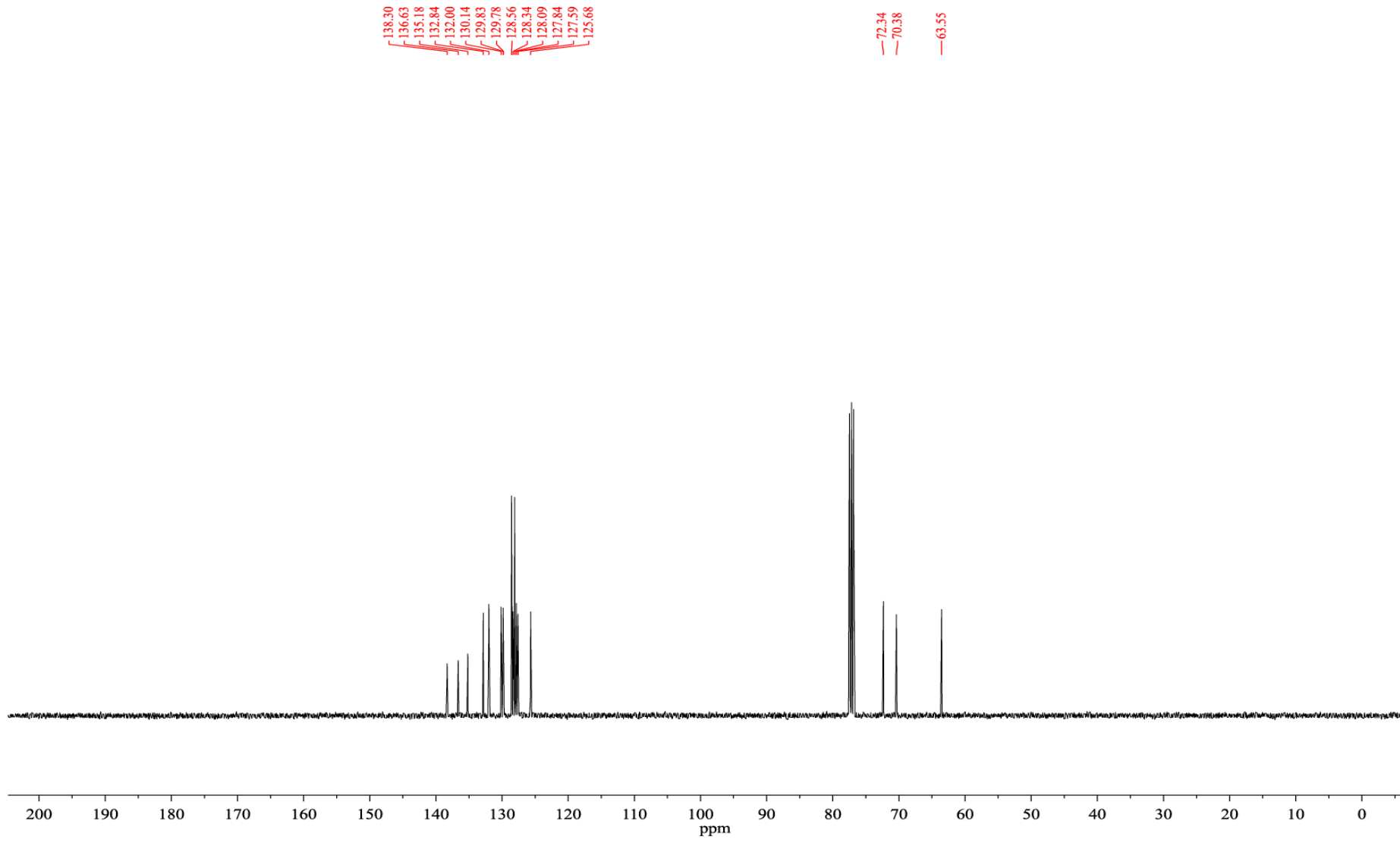


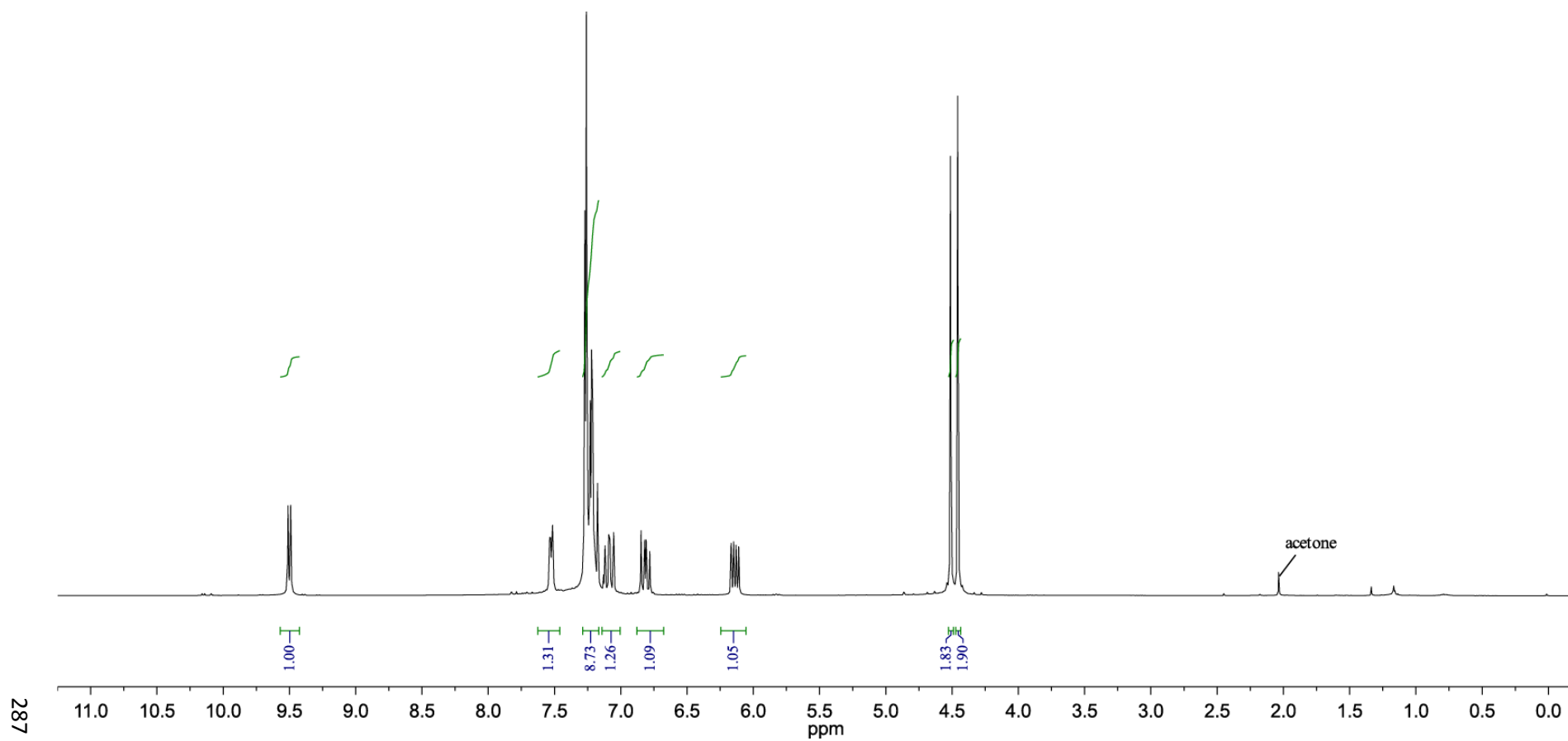
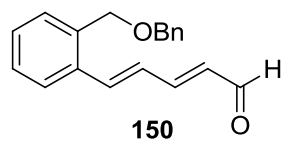


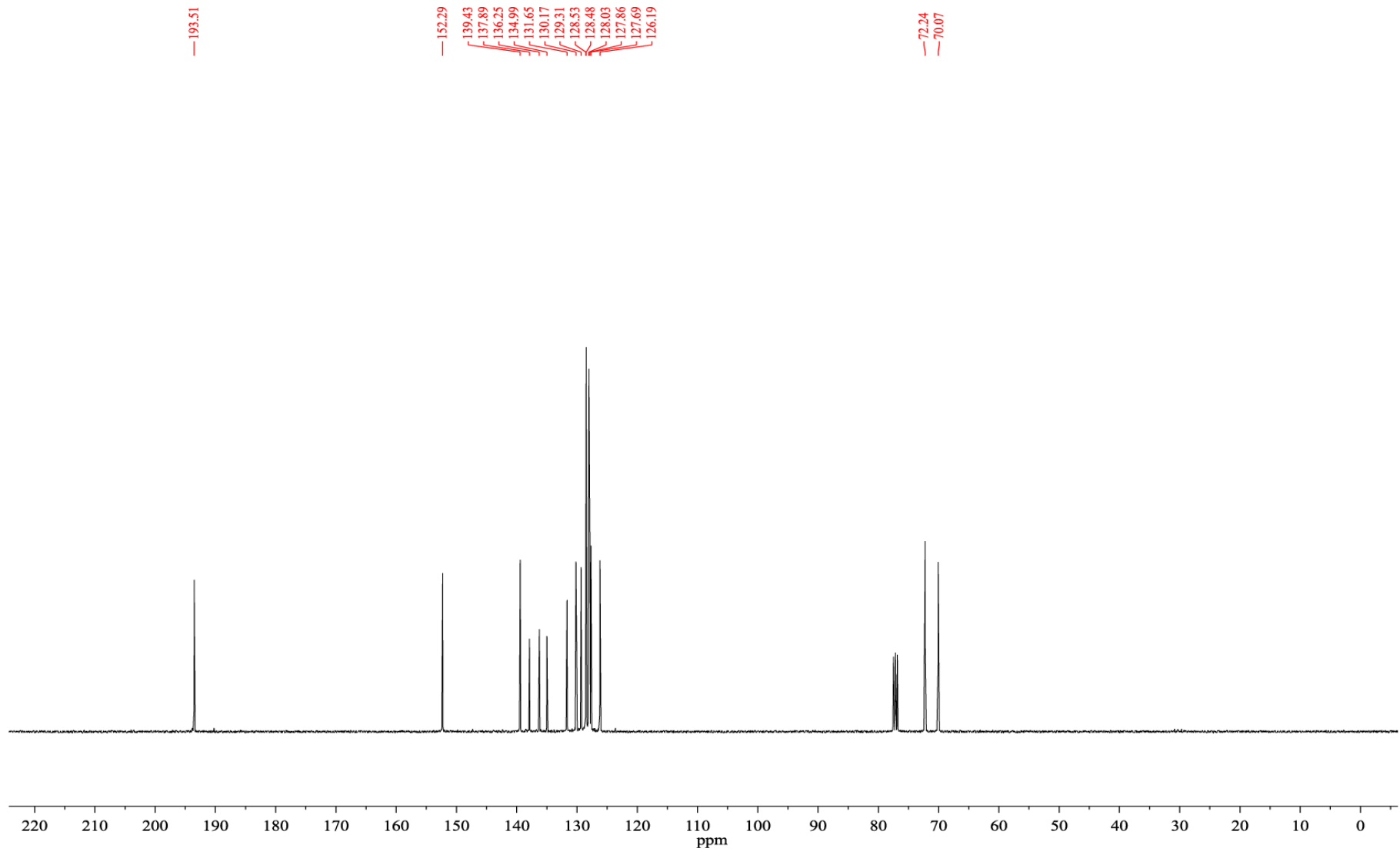


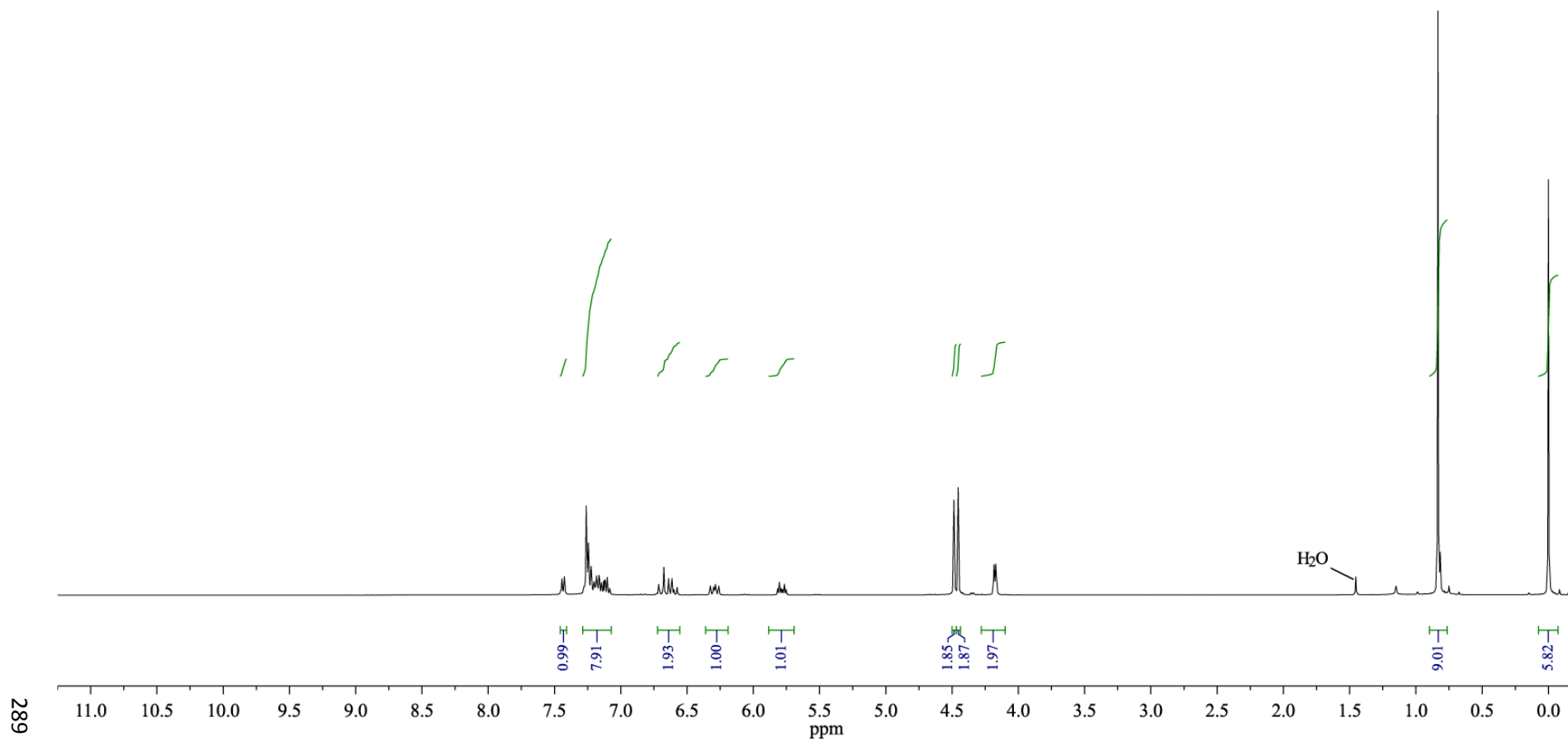
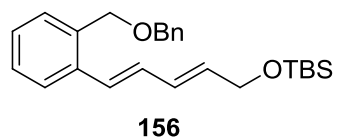
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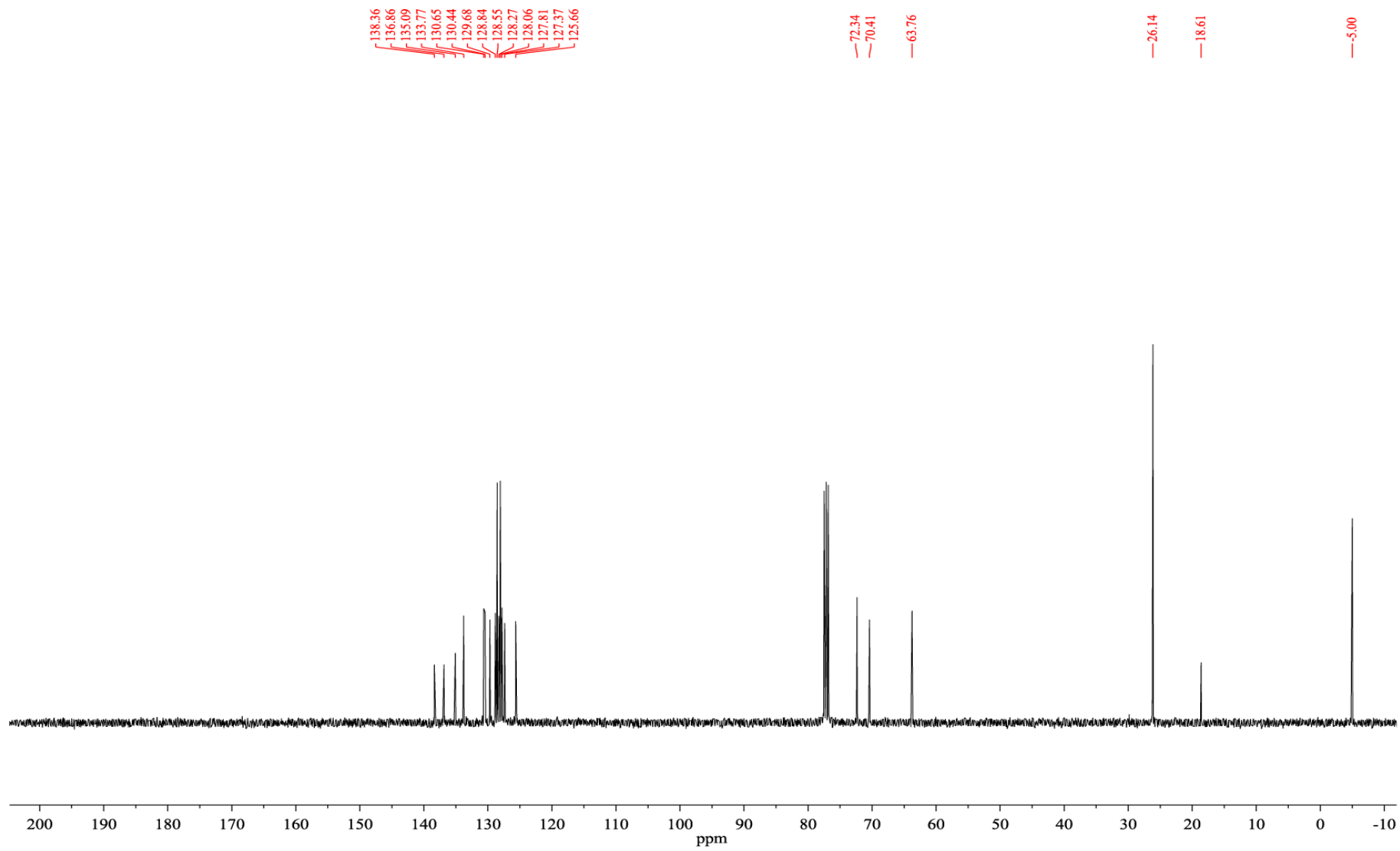


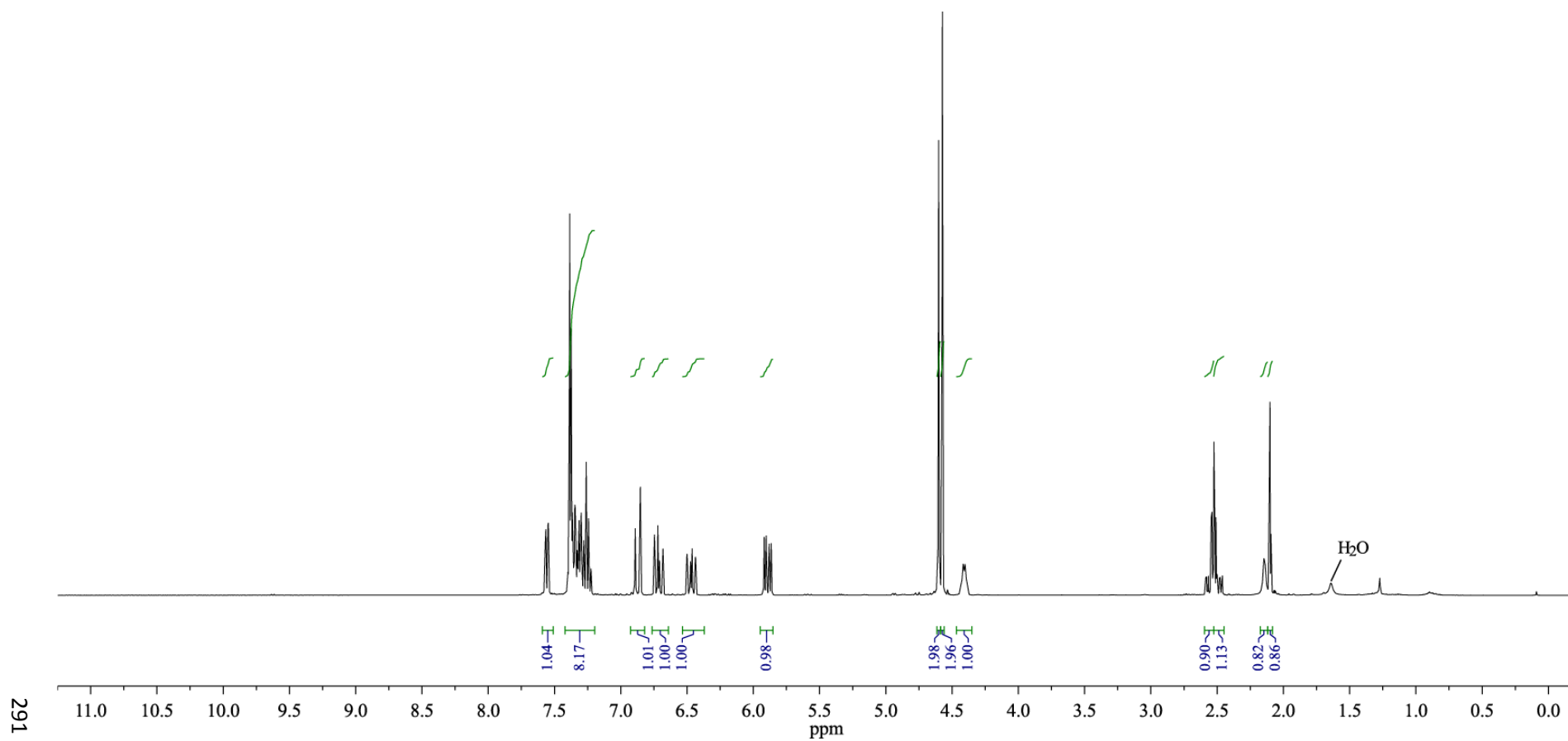
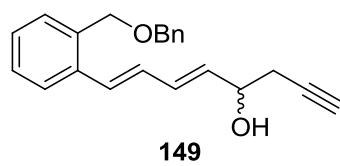


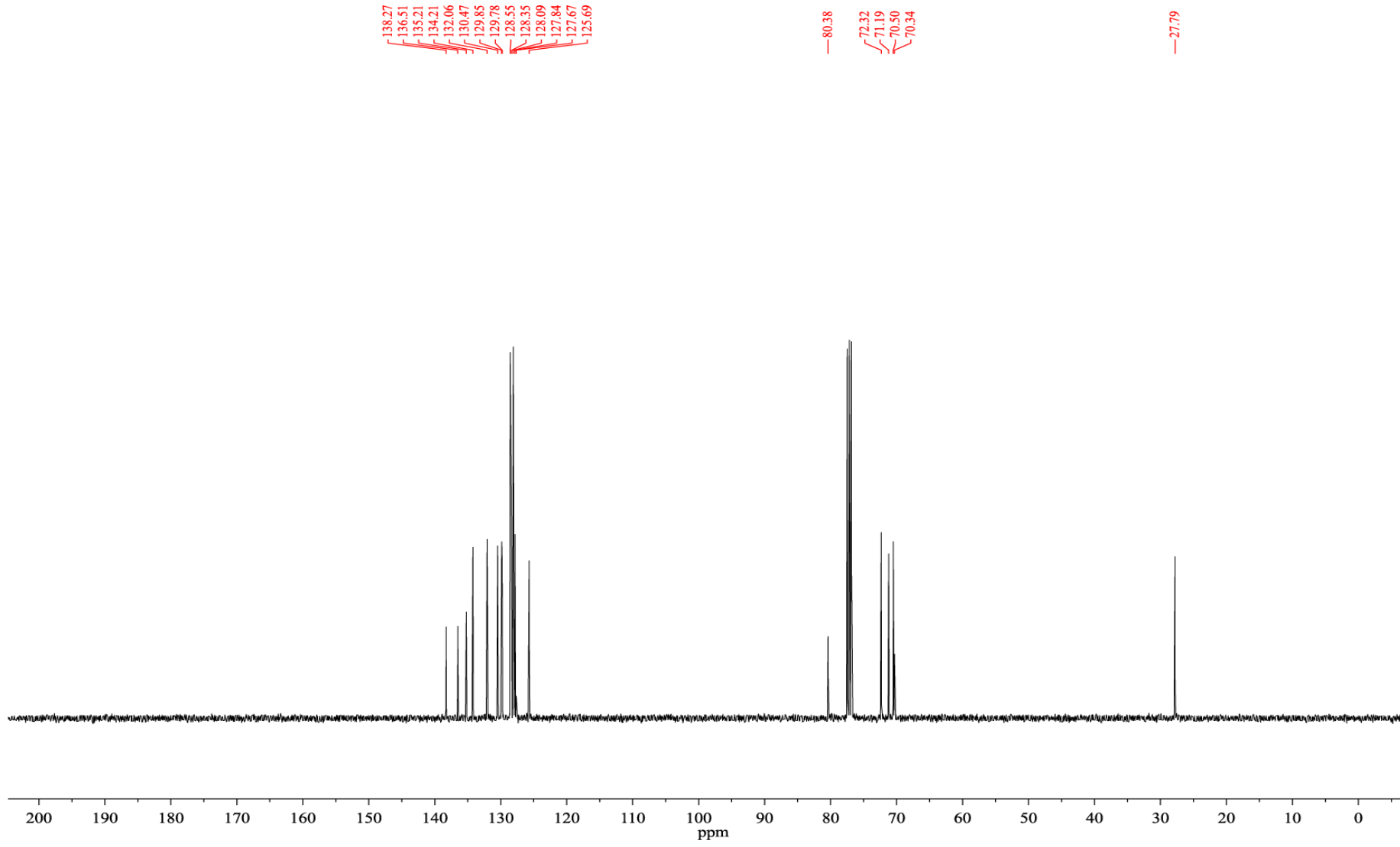


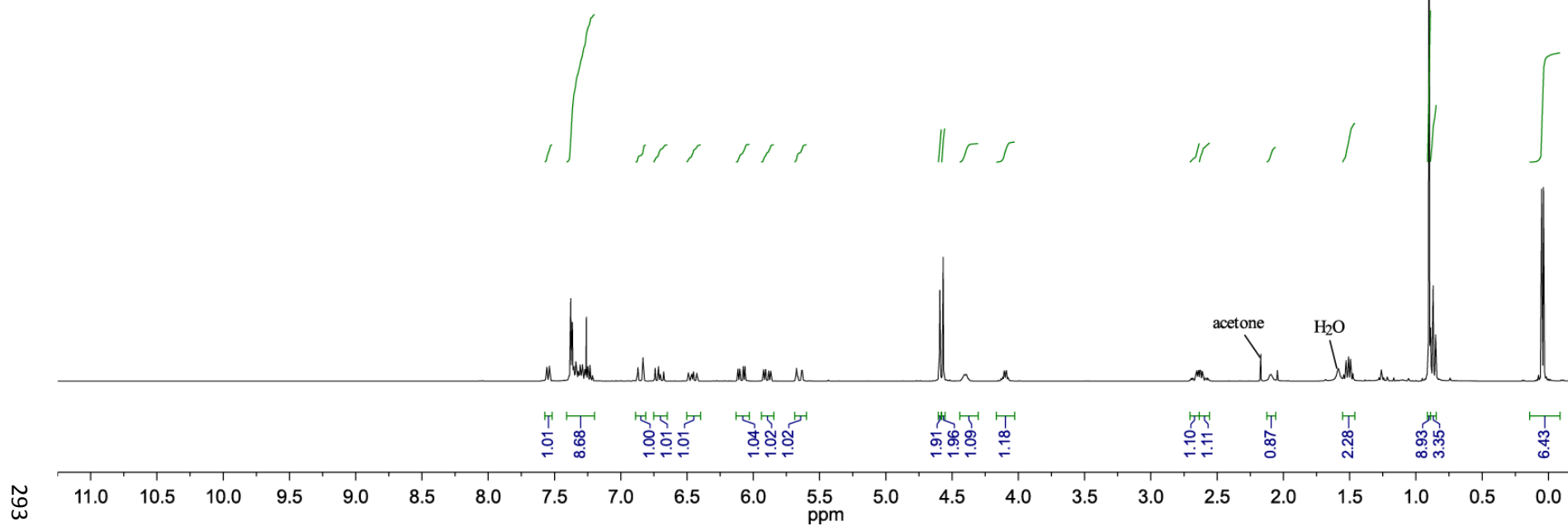
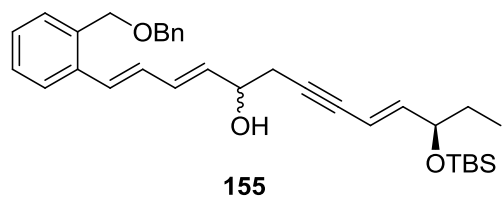


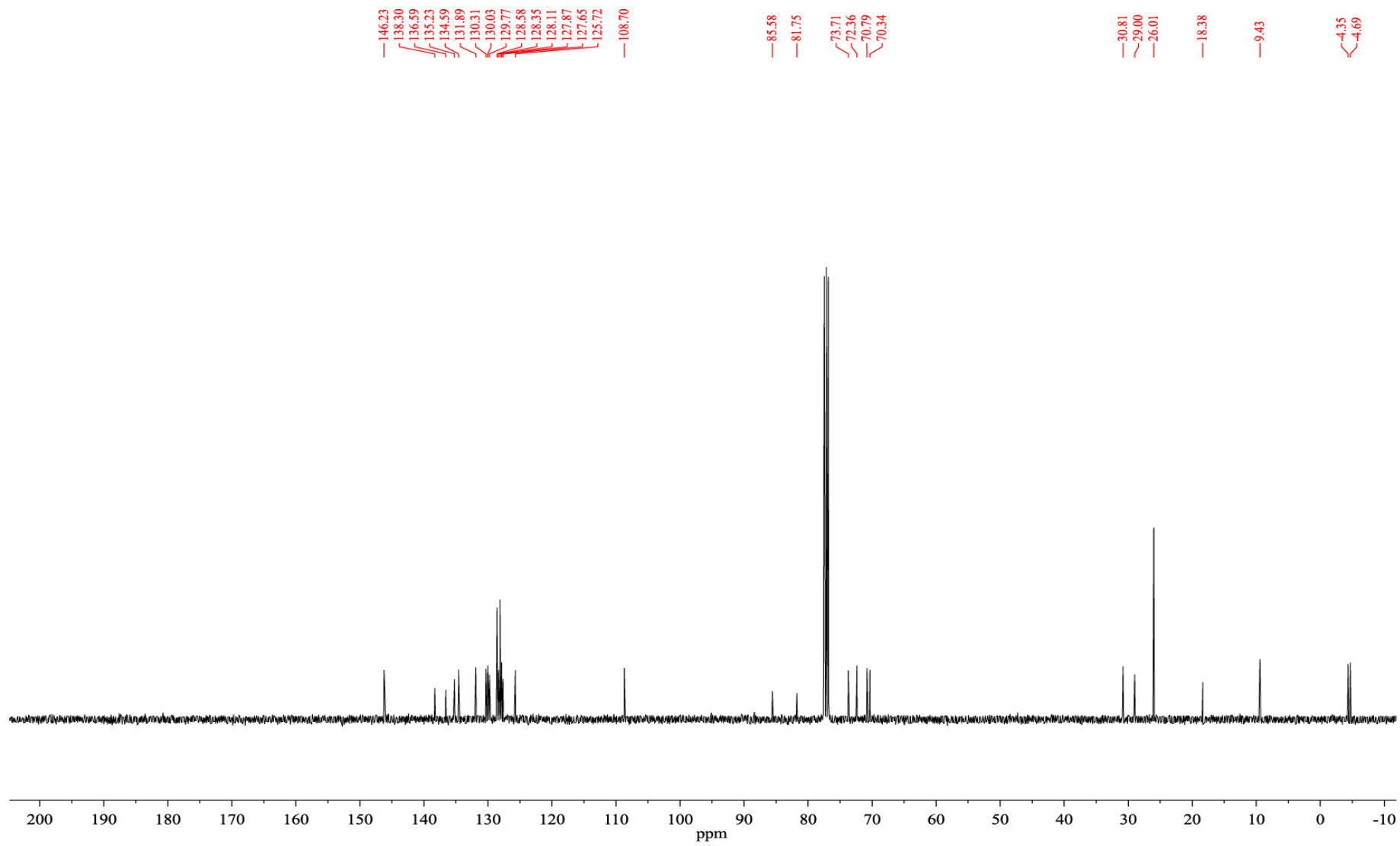


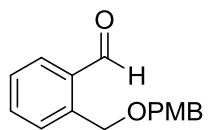




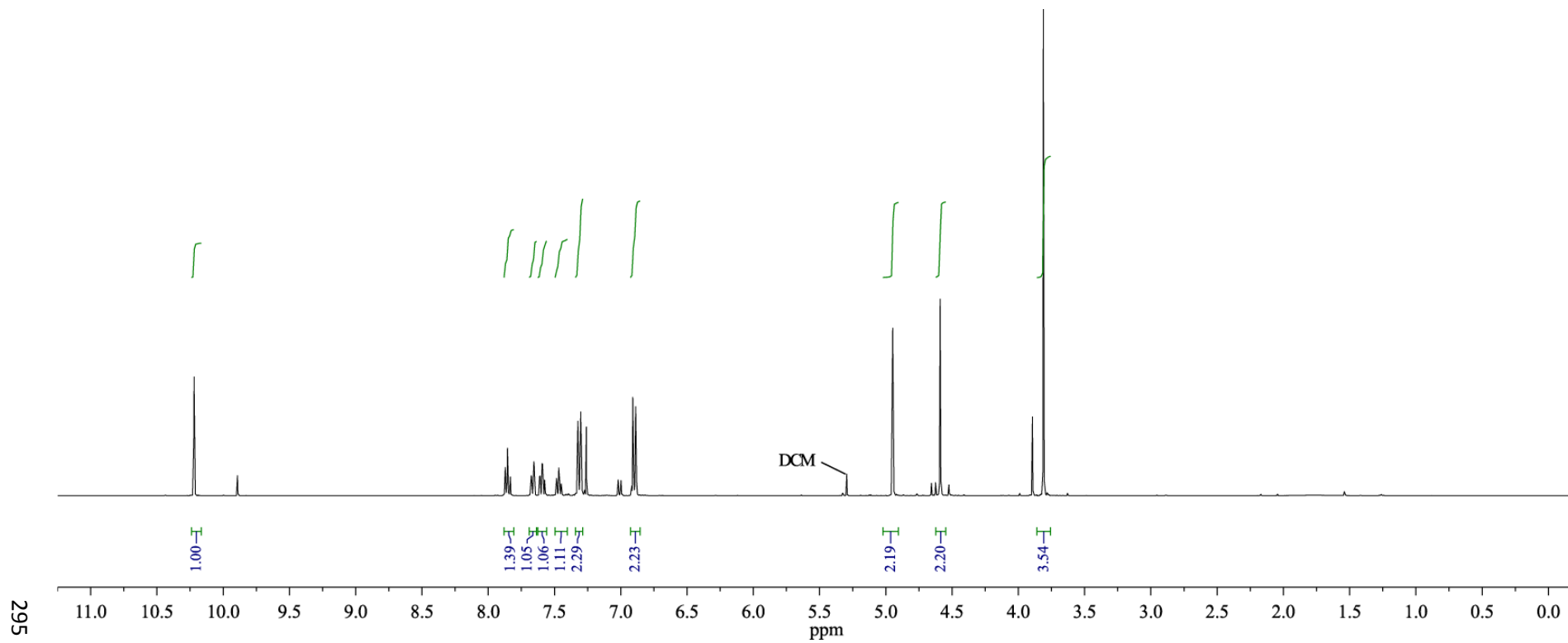


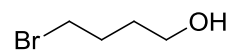




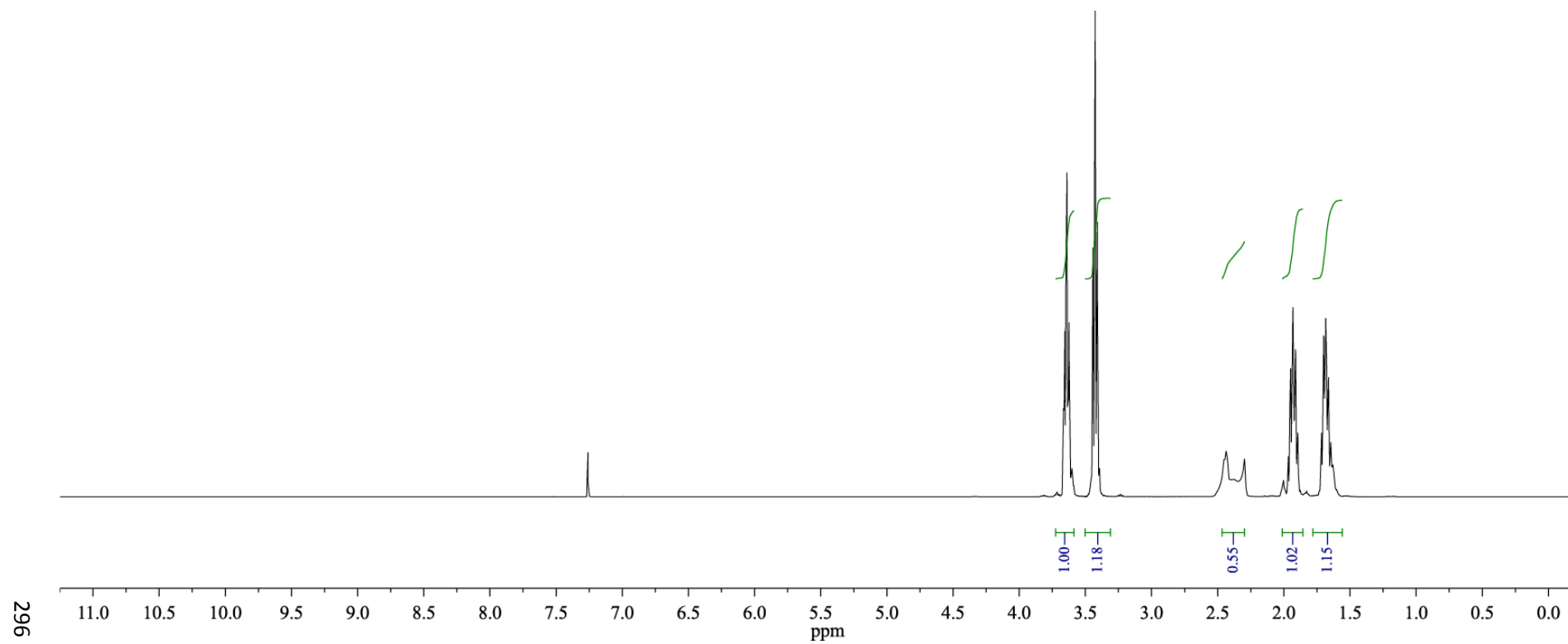


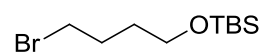
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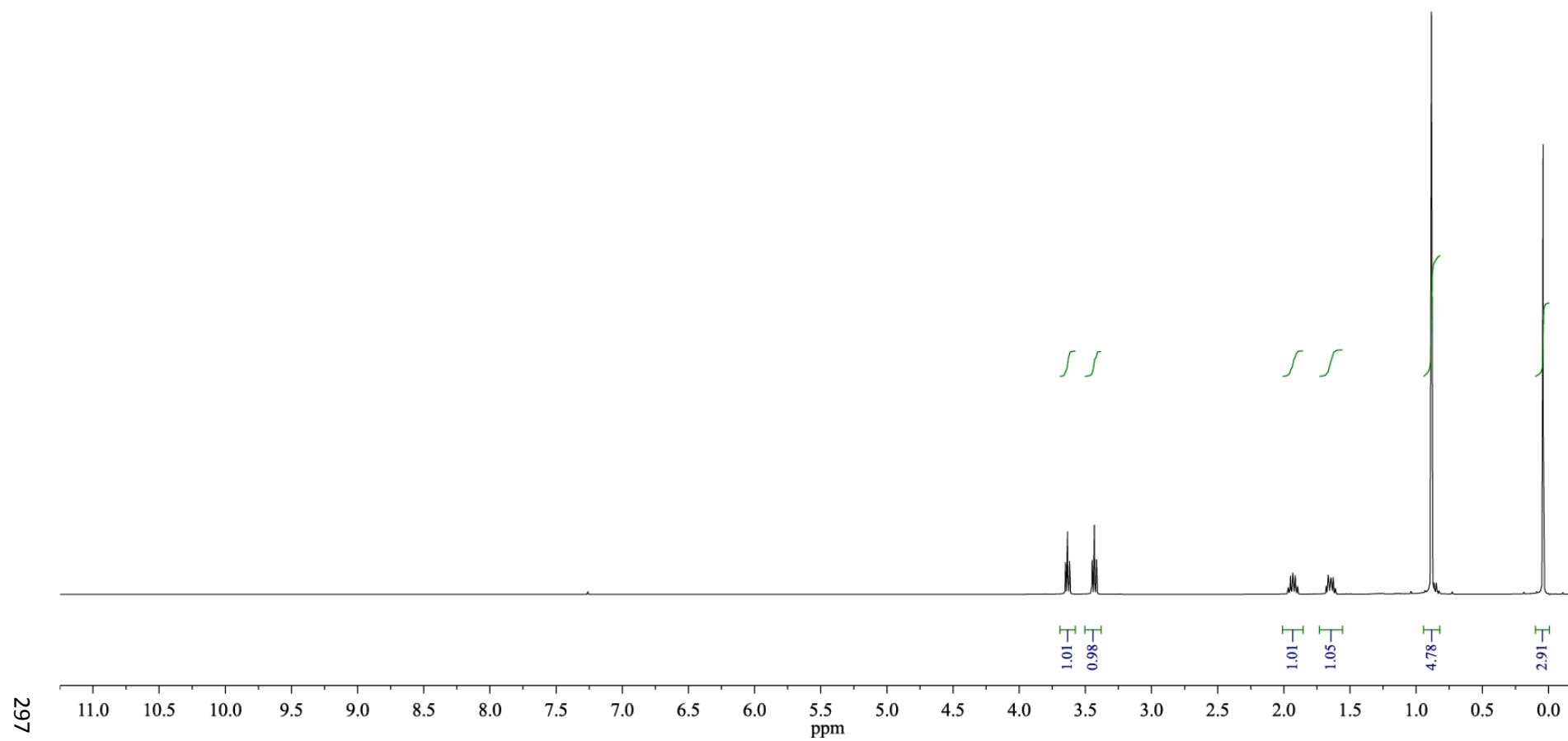


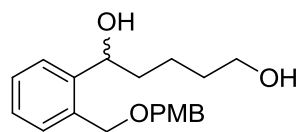
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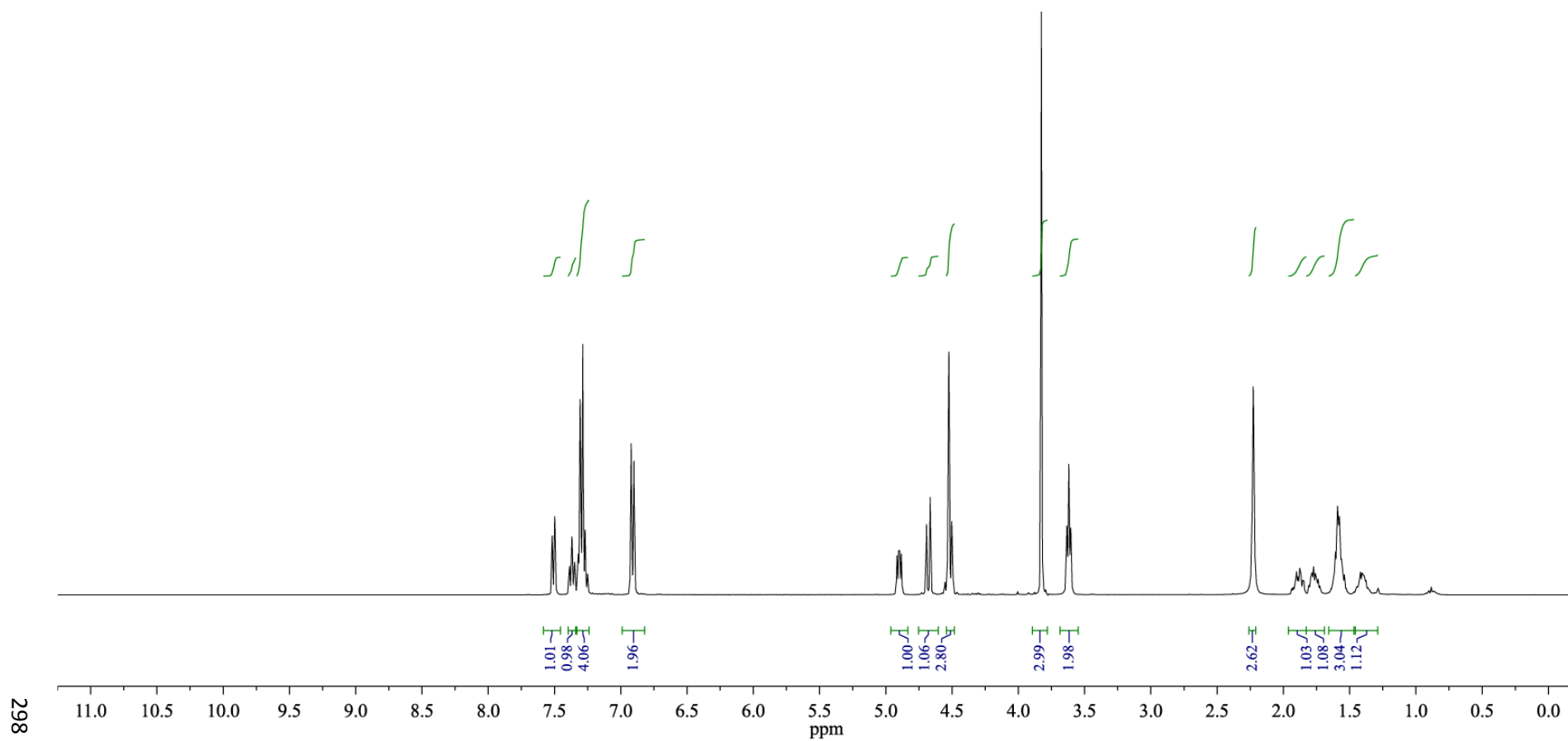


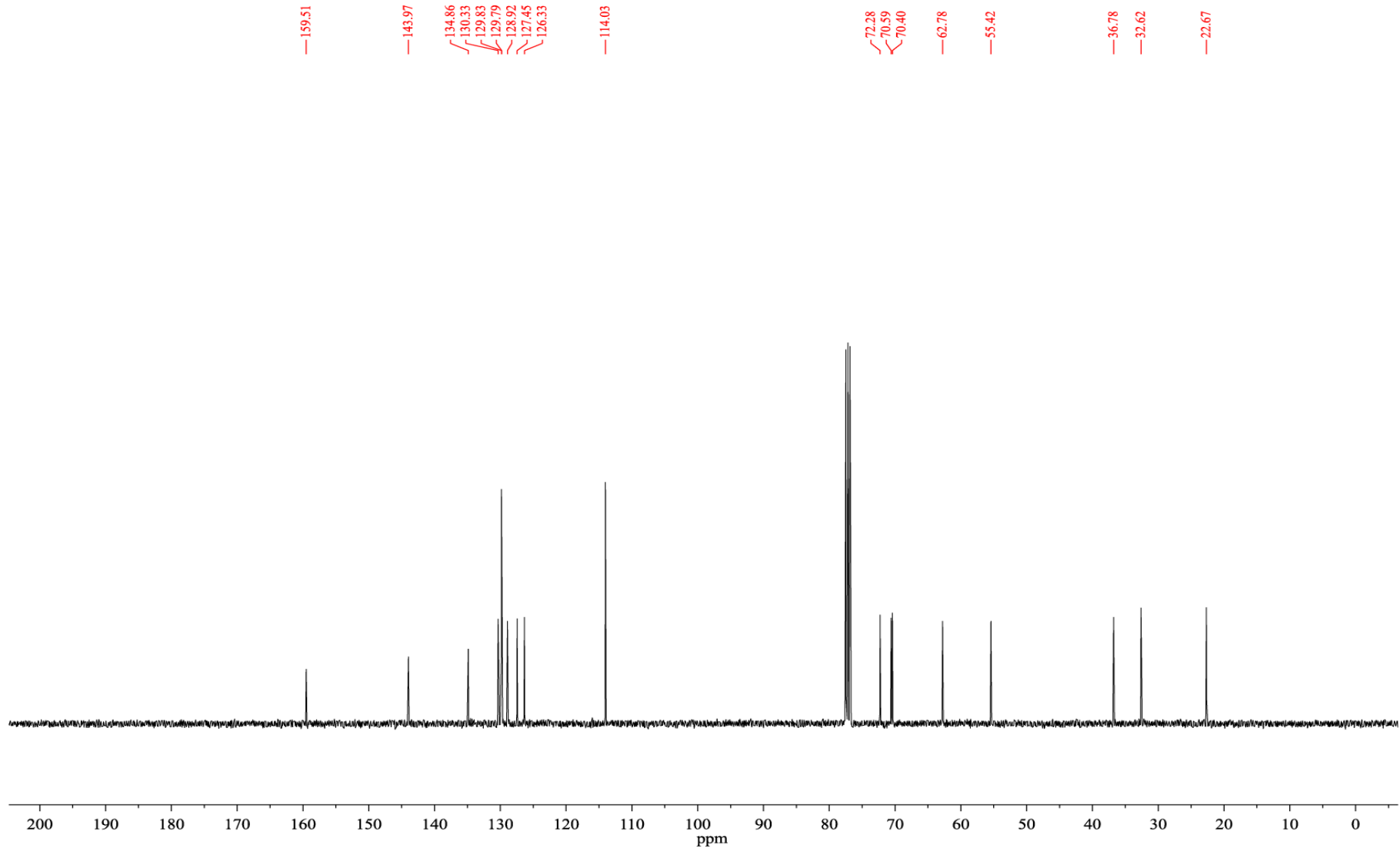
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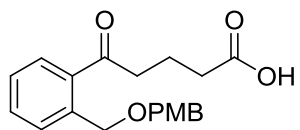




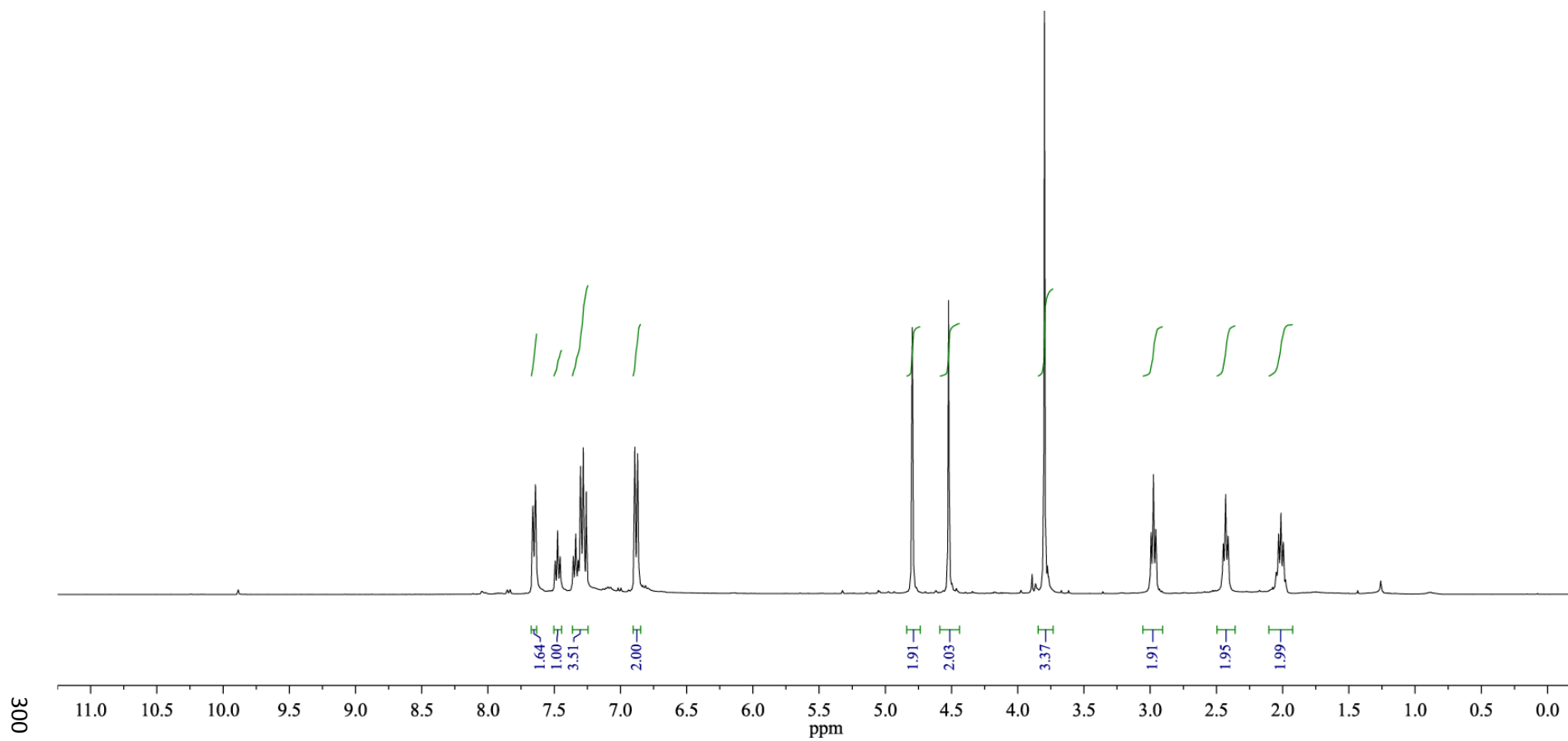
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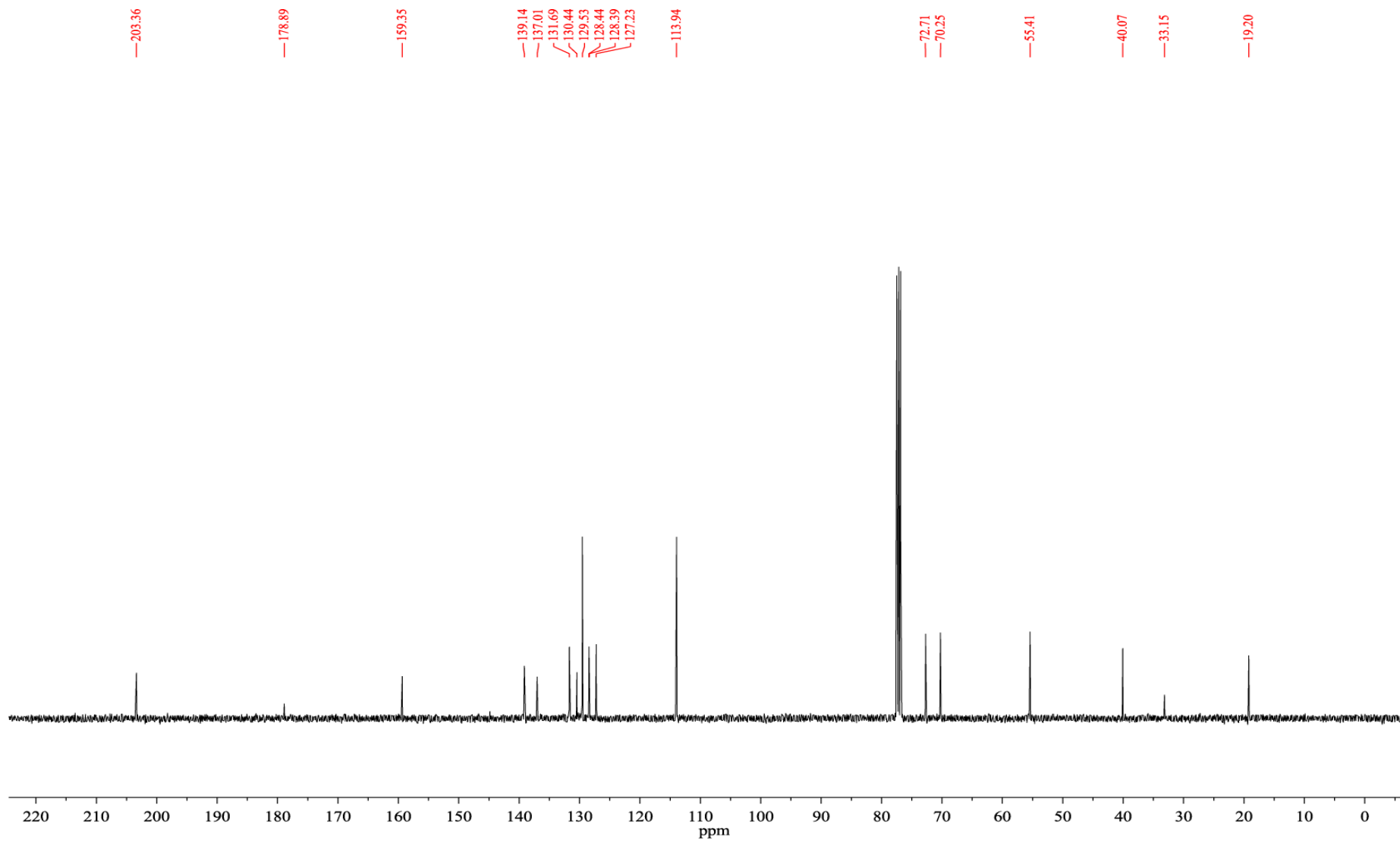


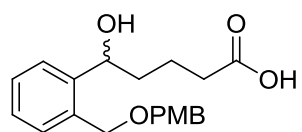




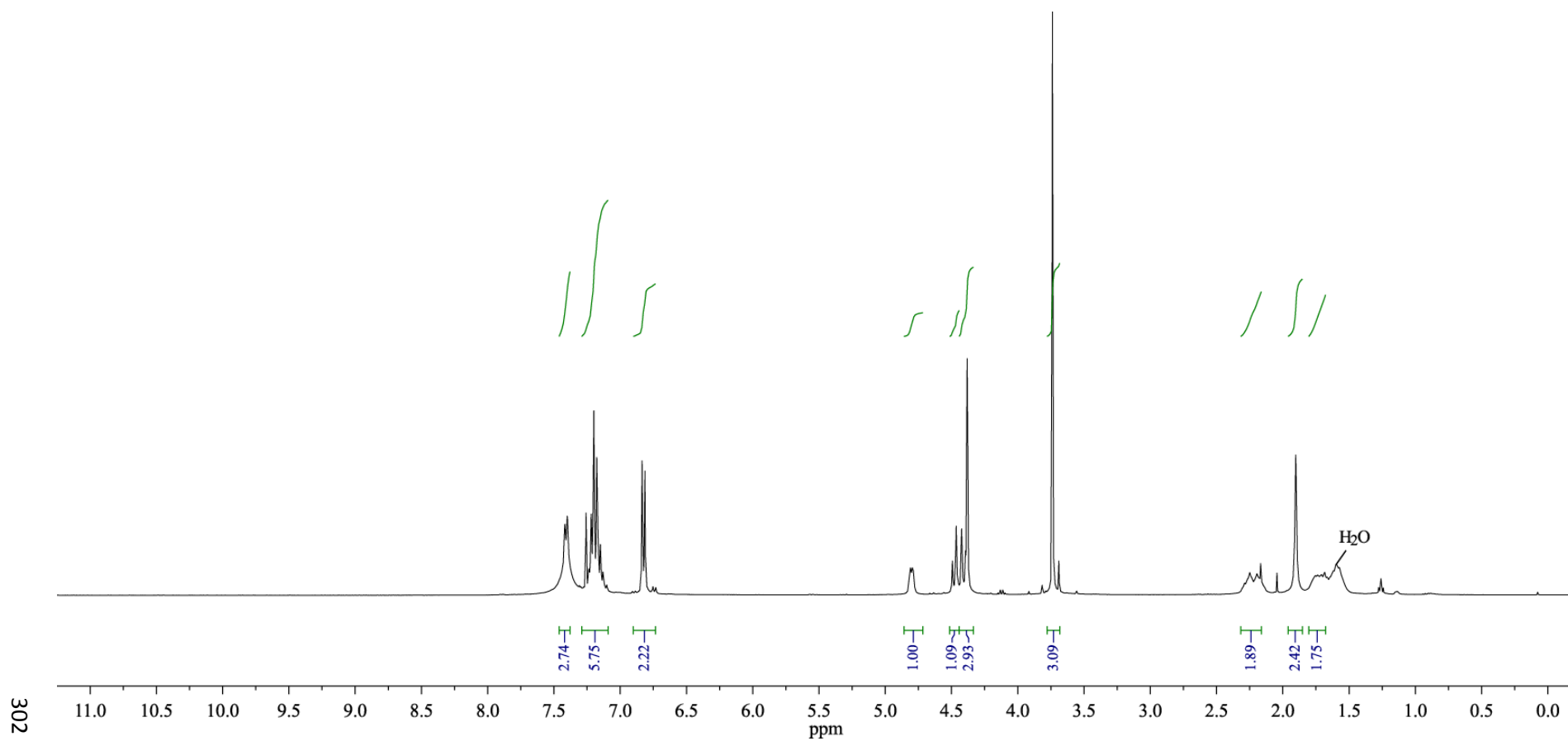
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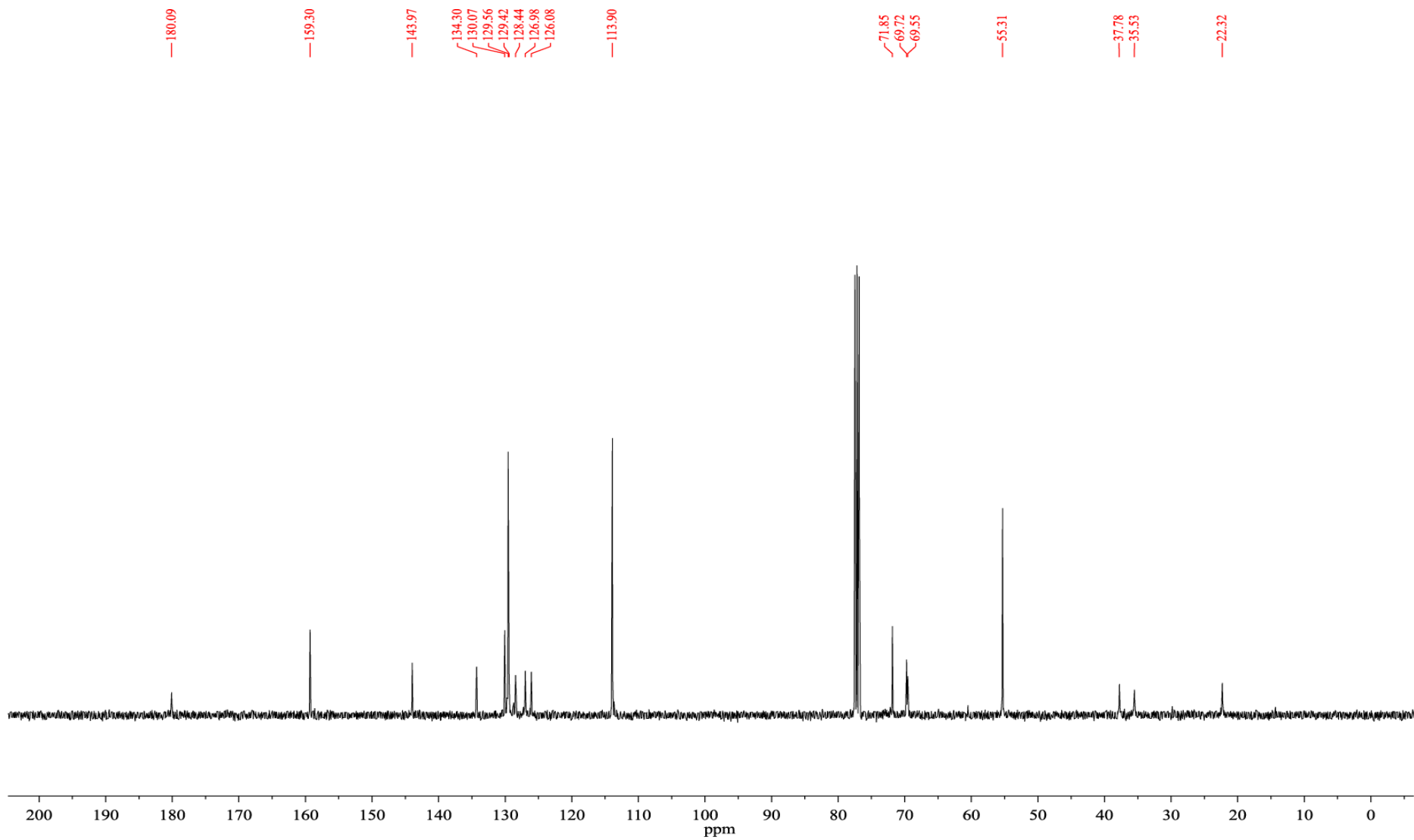


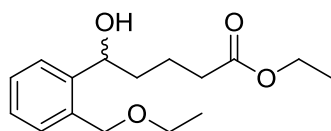




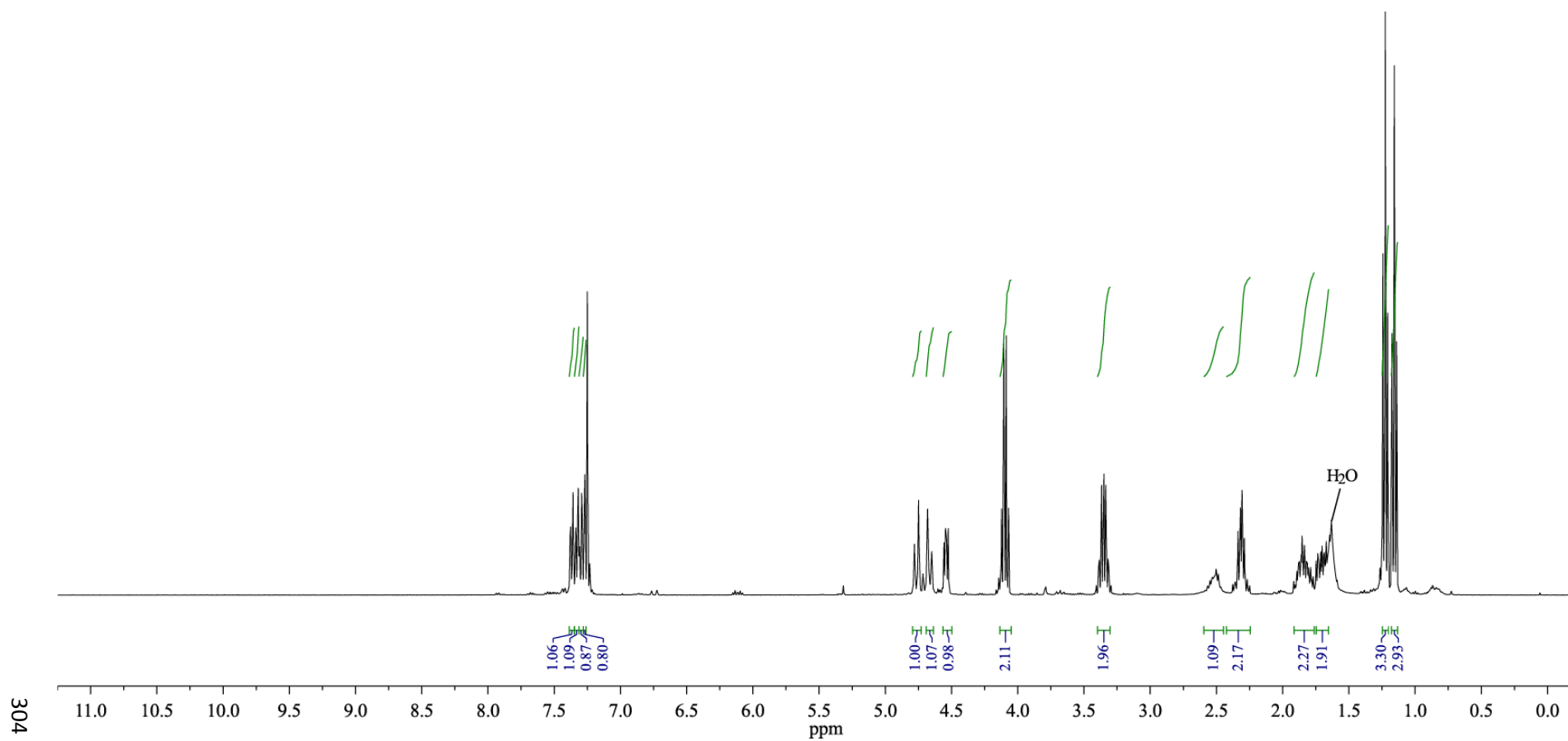
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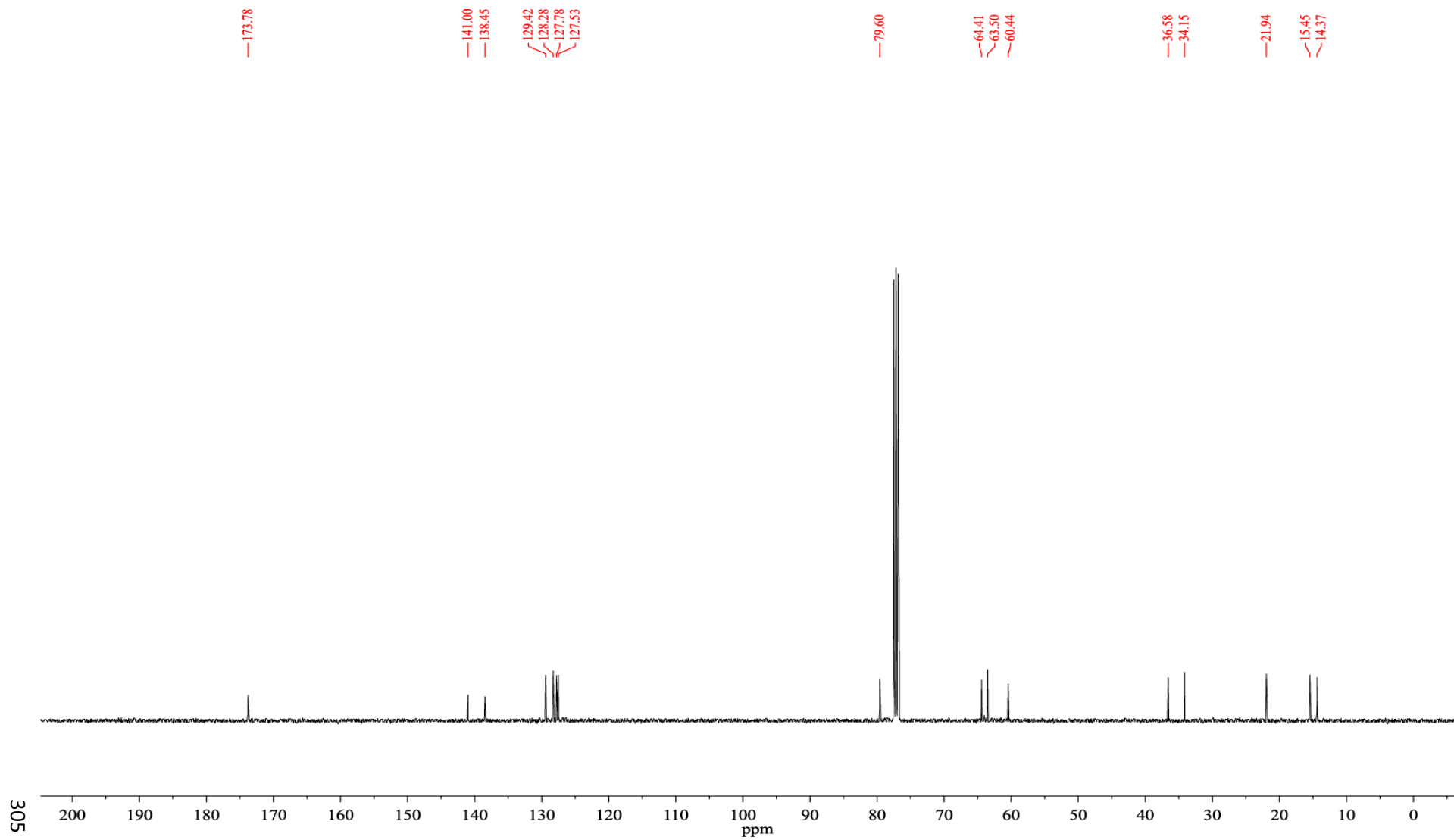


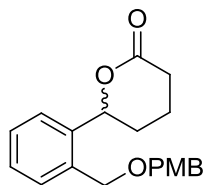




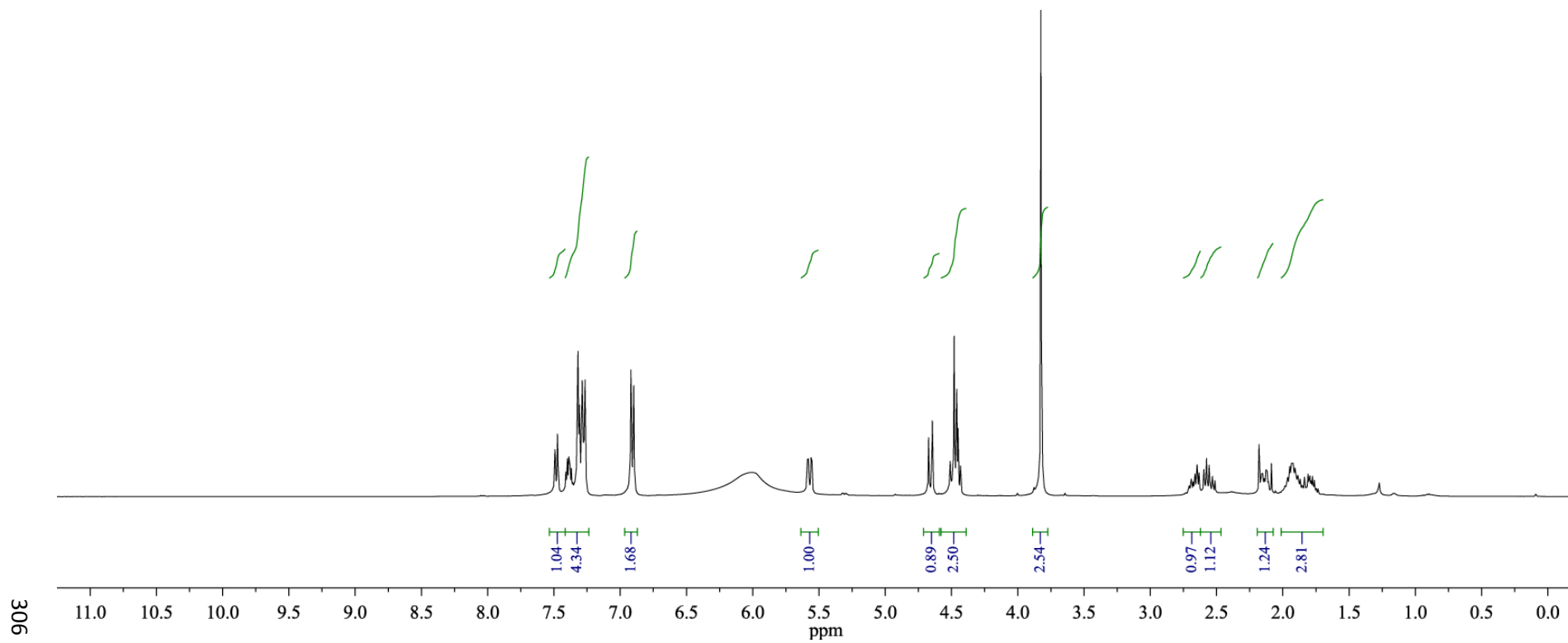
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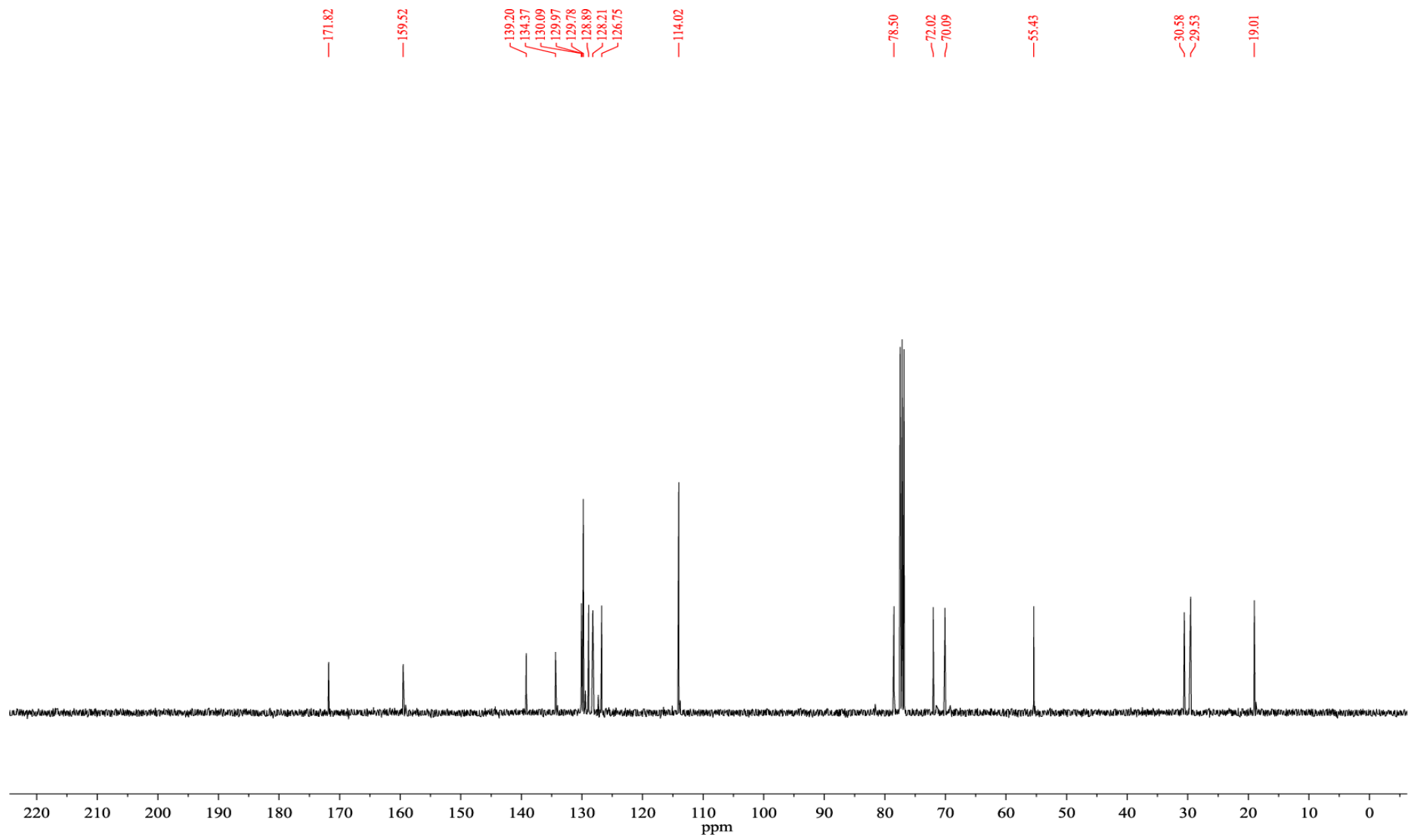




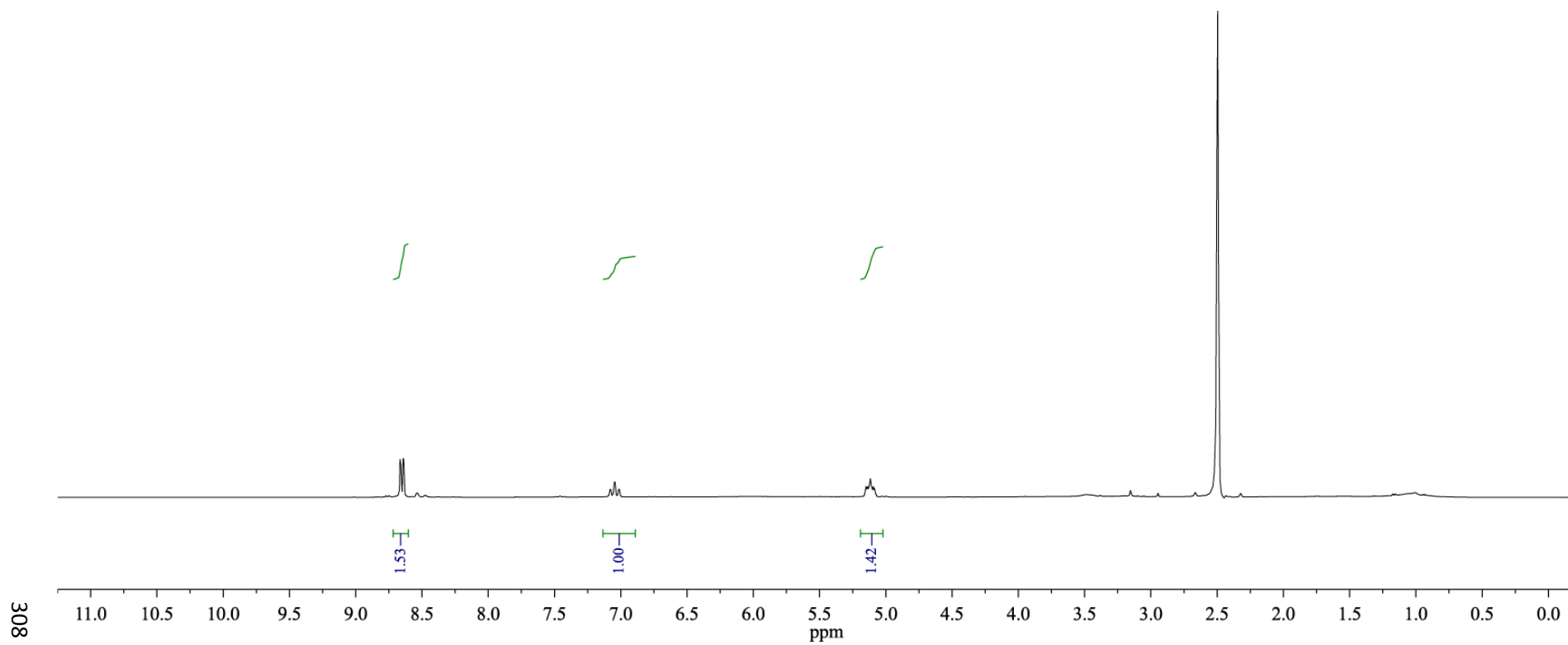
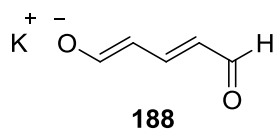


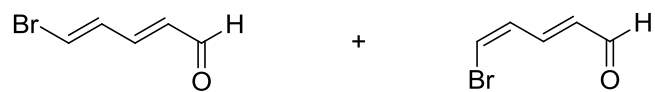
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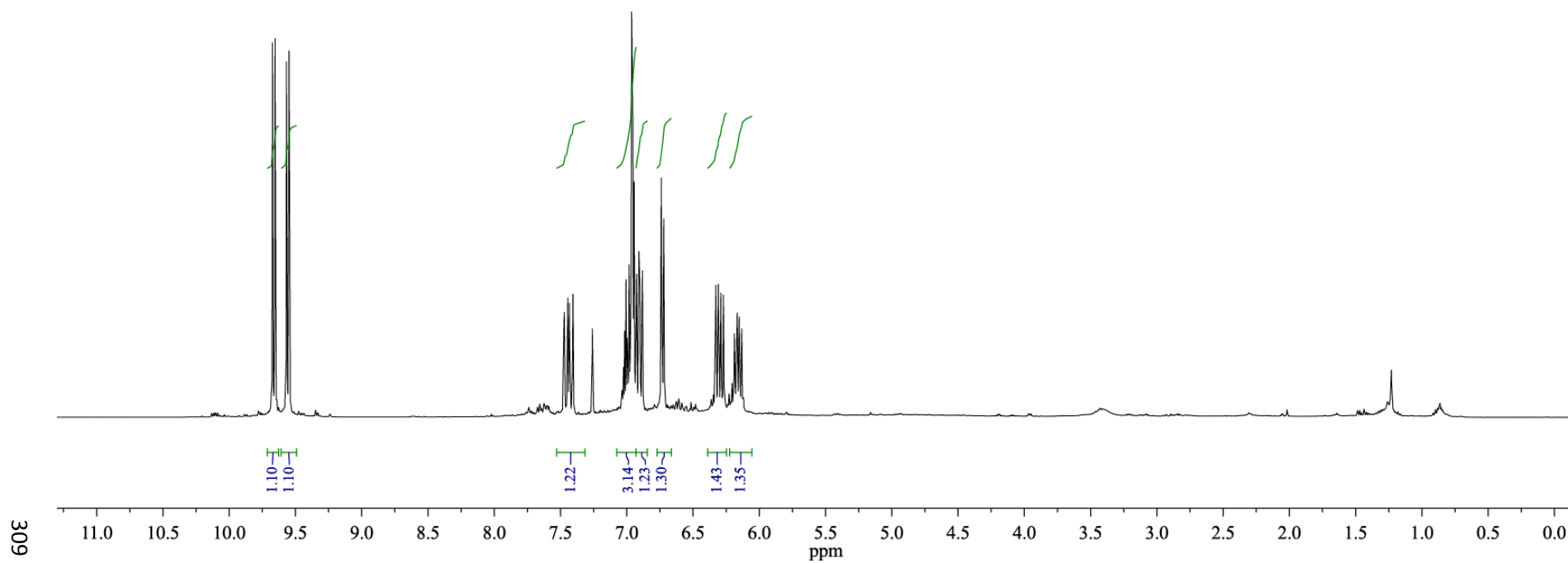
Chapter 4 spectra

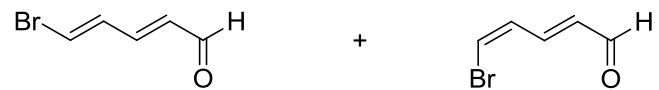




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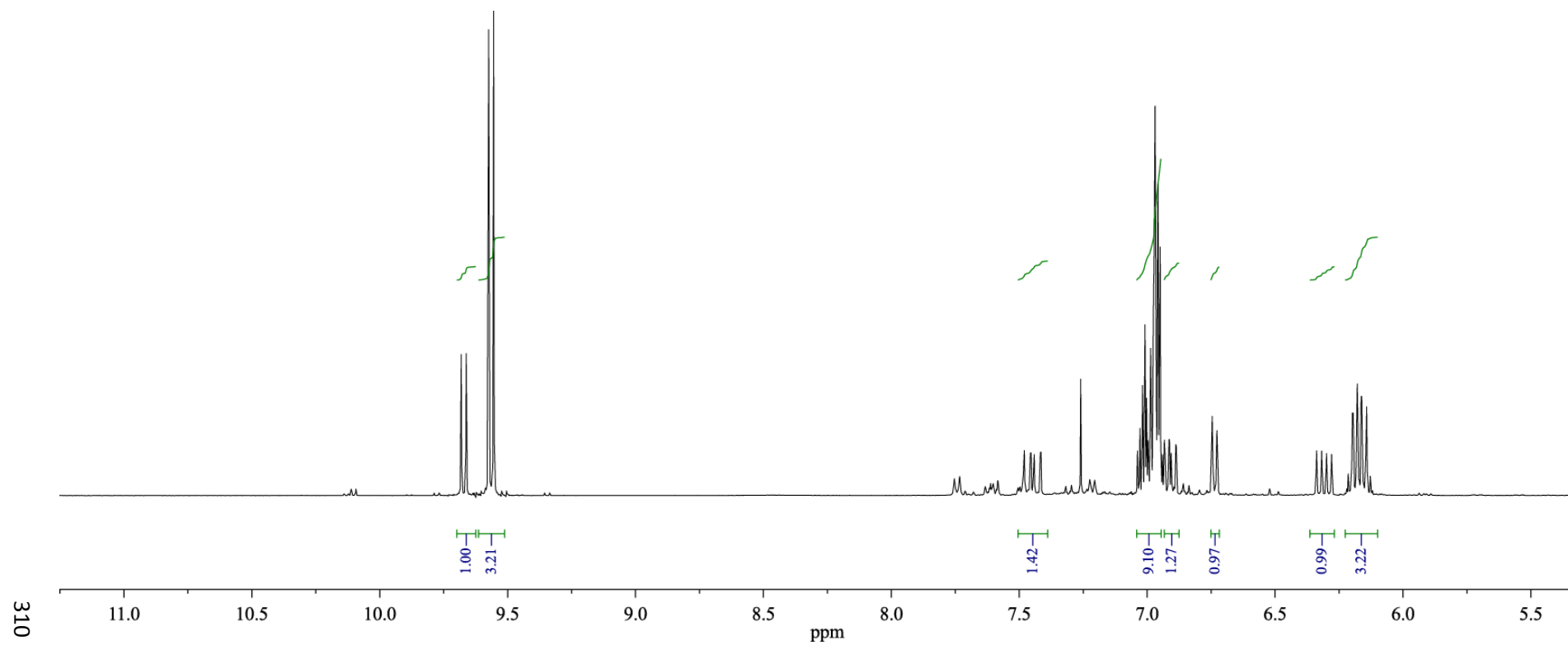
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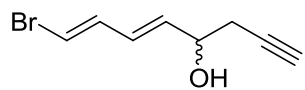




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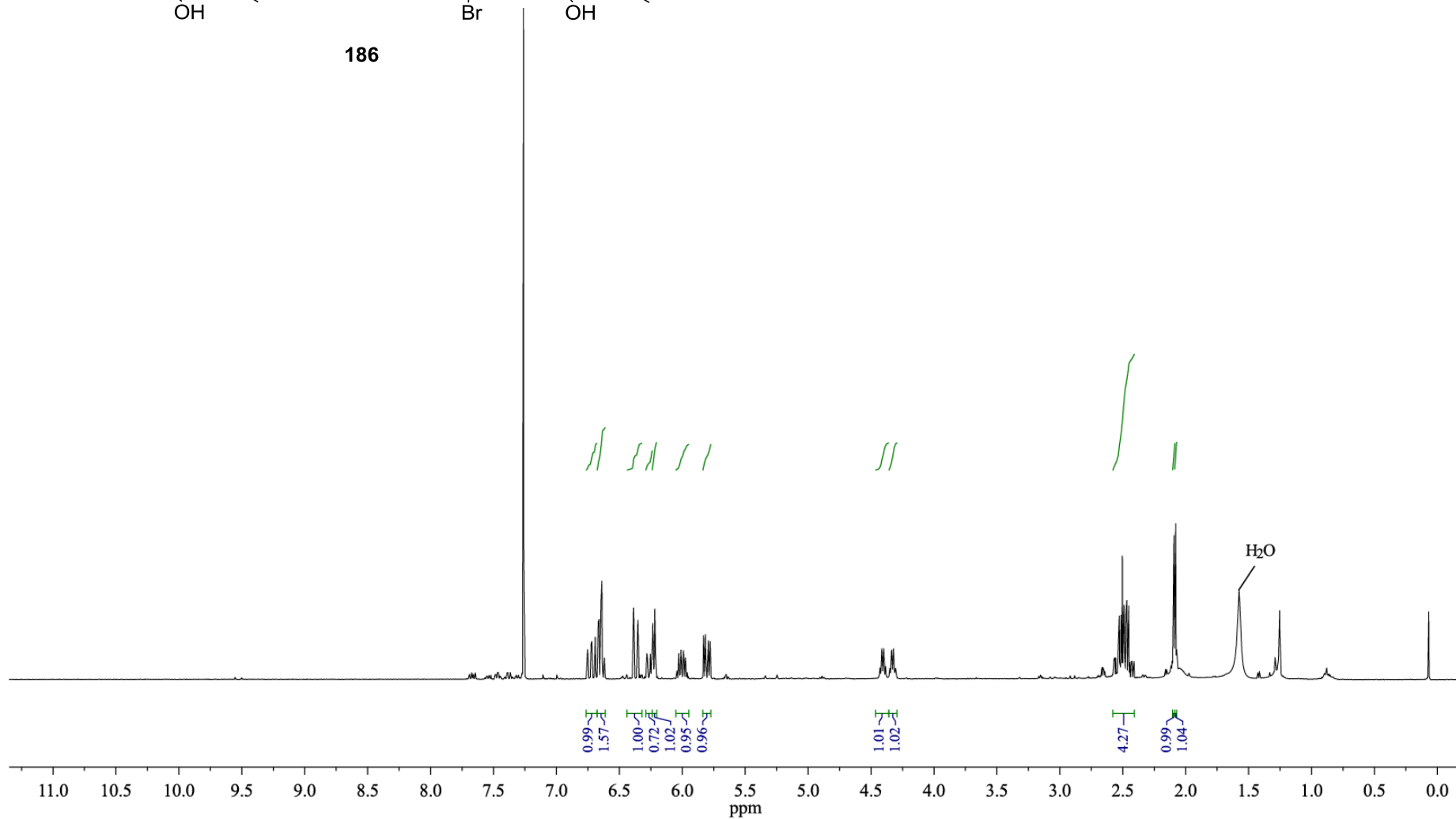
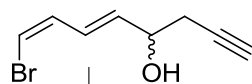
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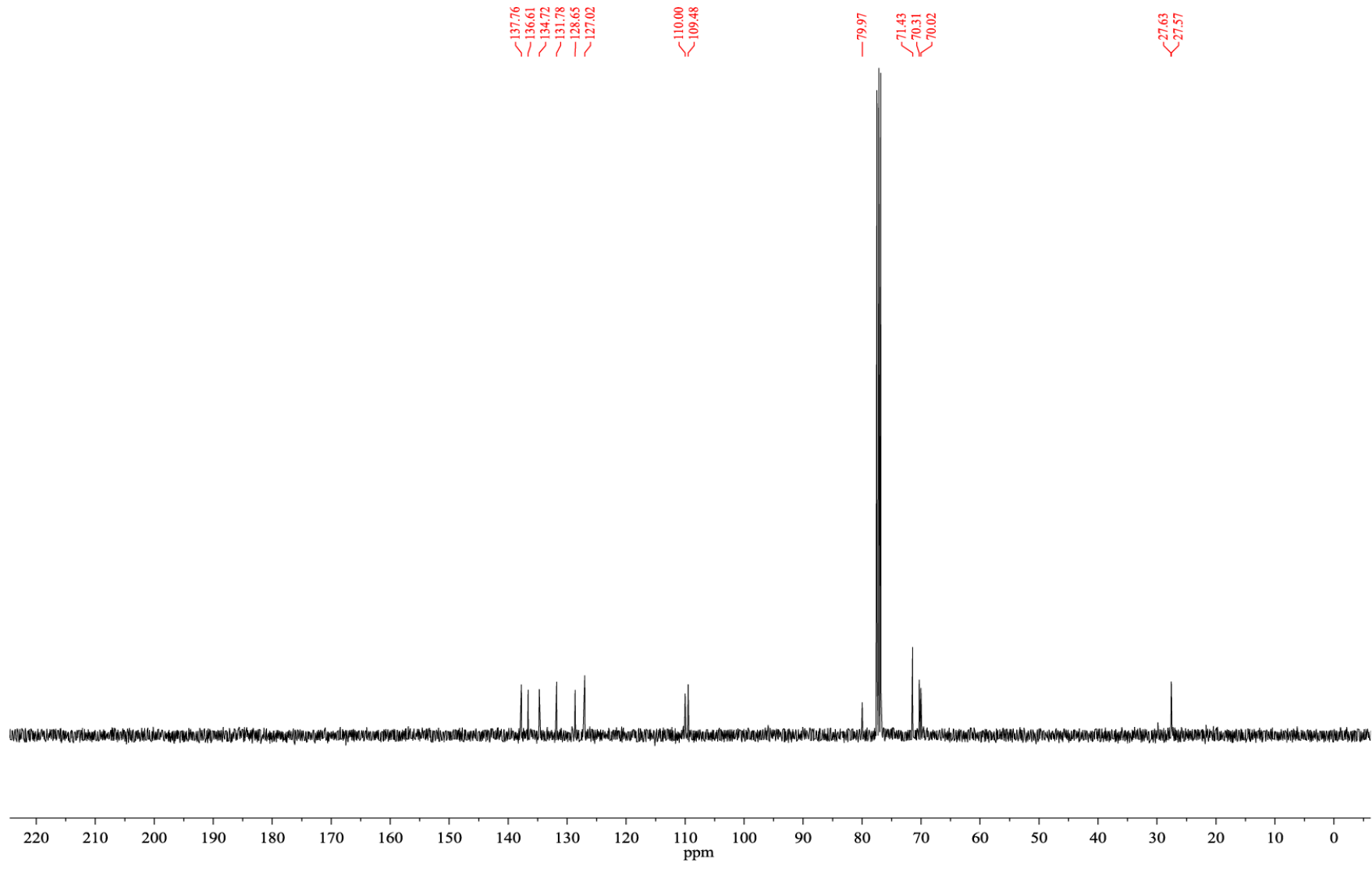


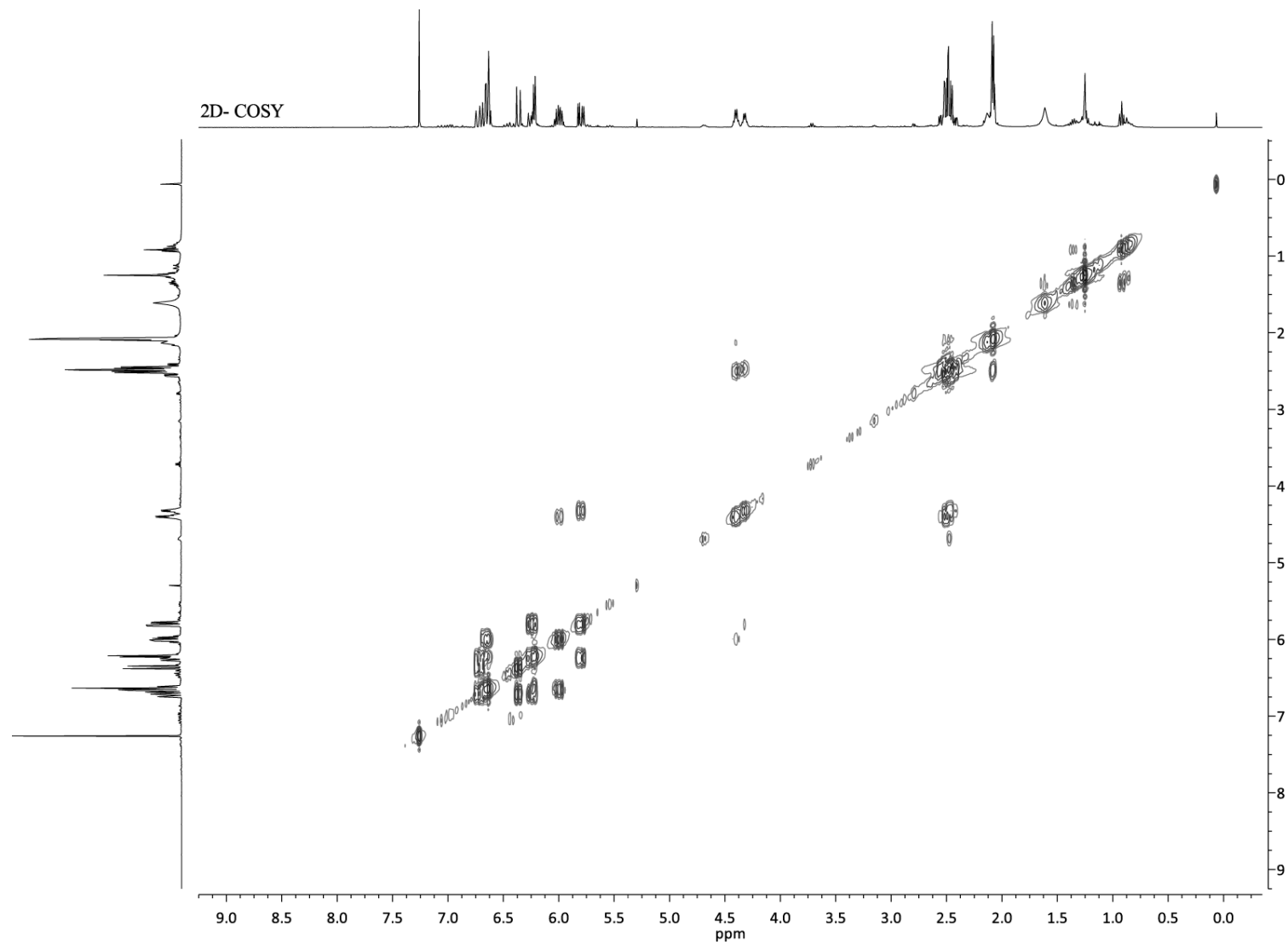


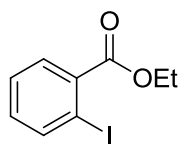
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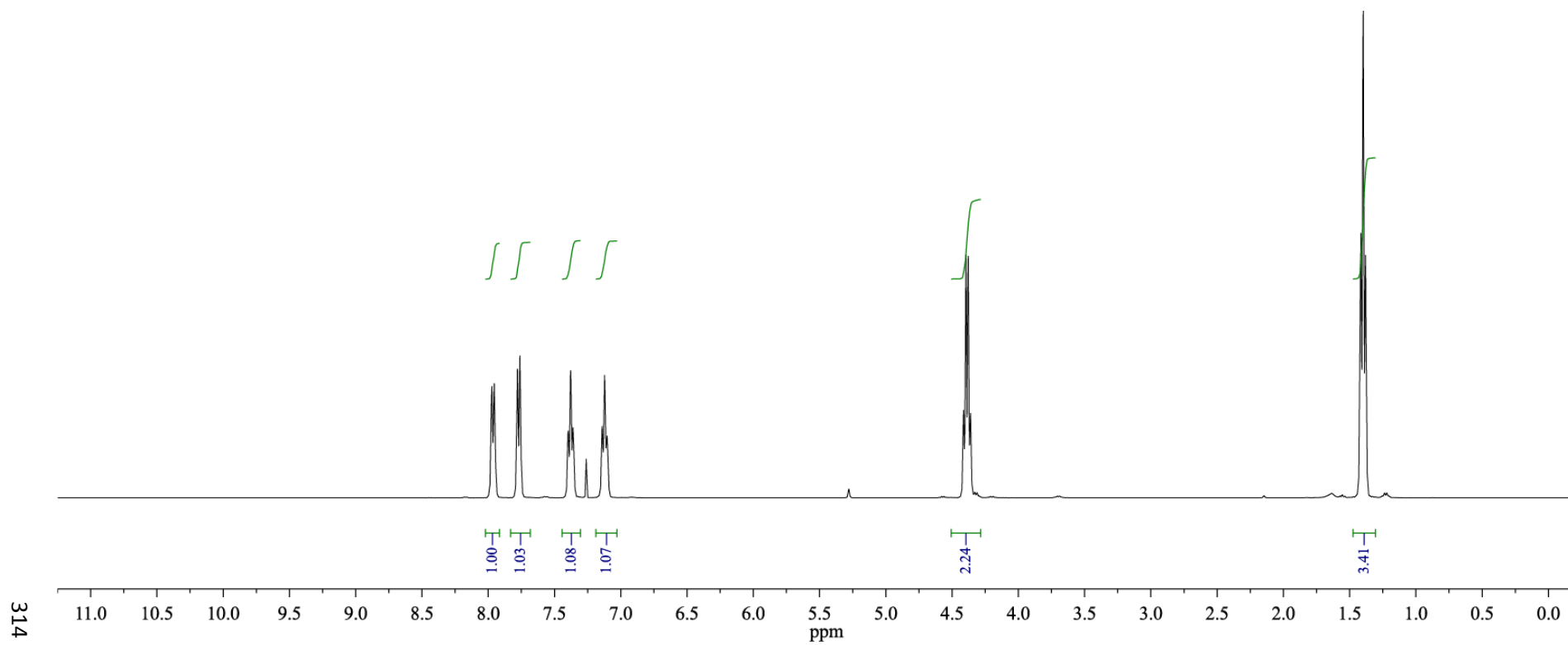


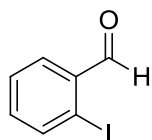




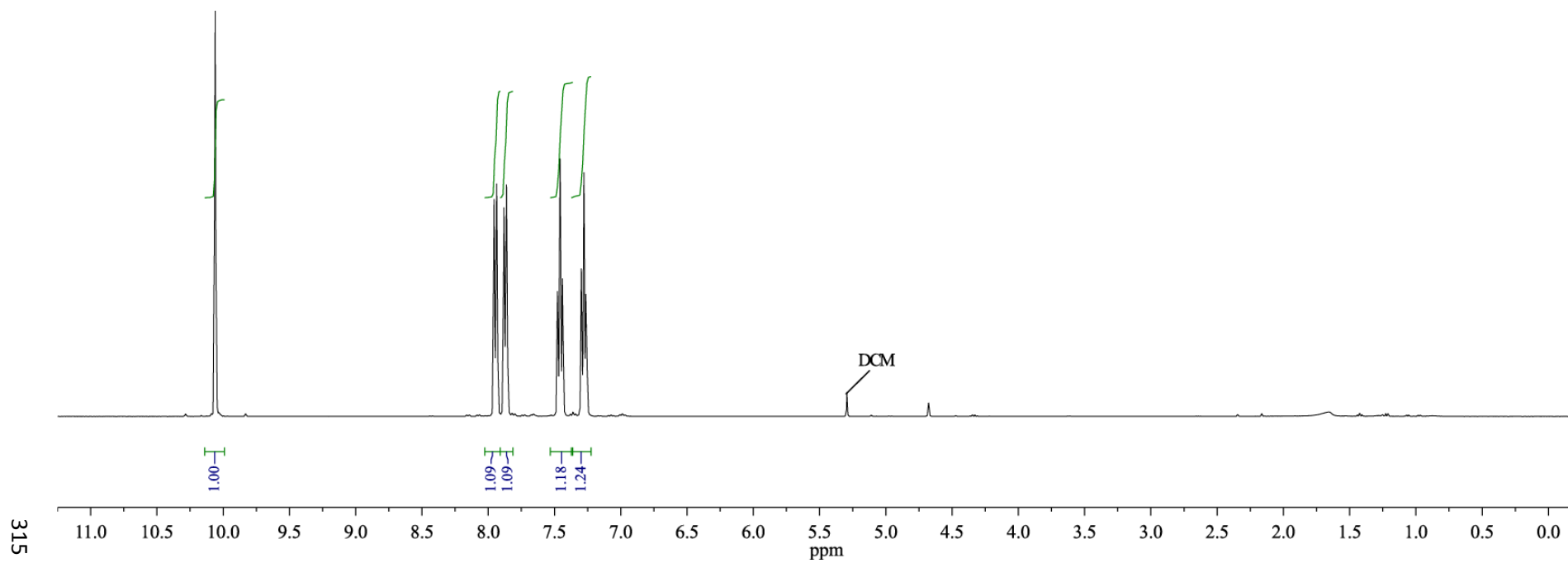


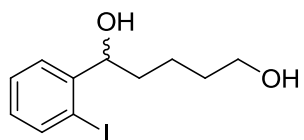
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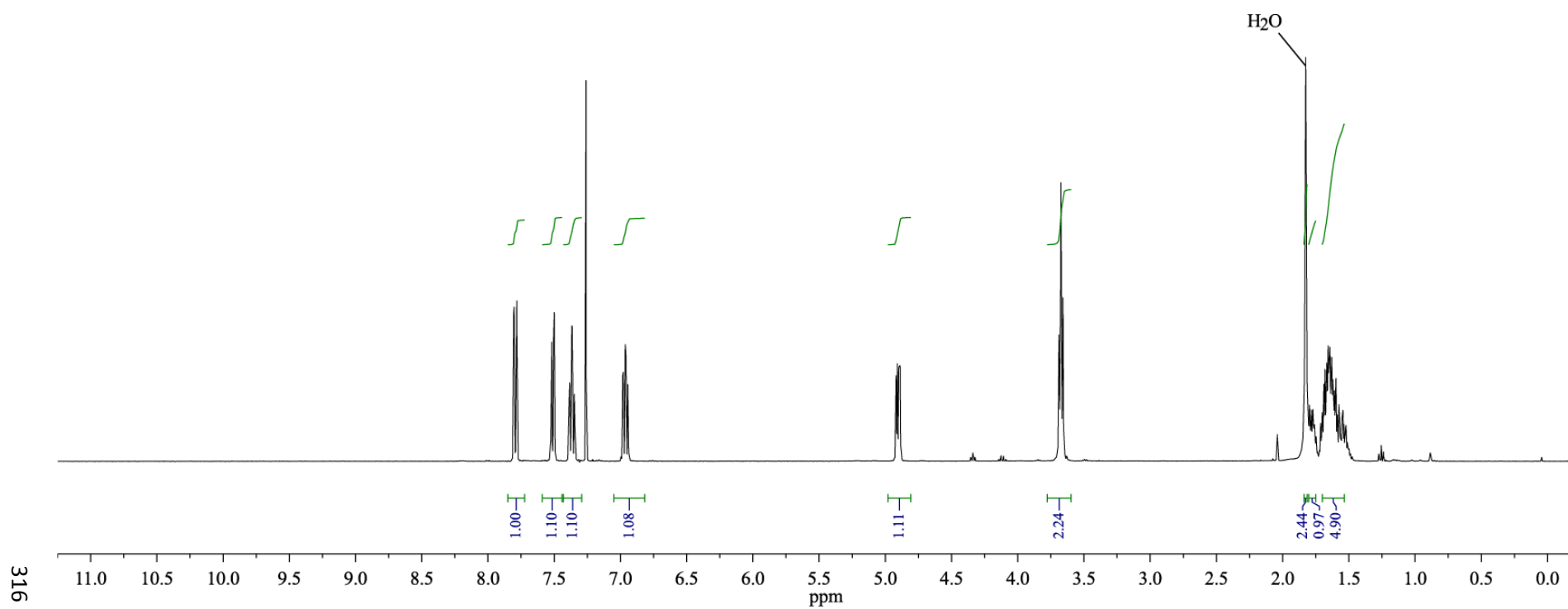


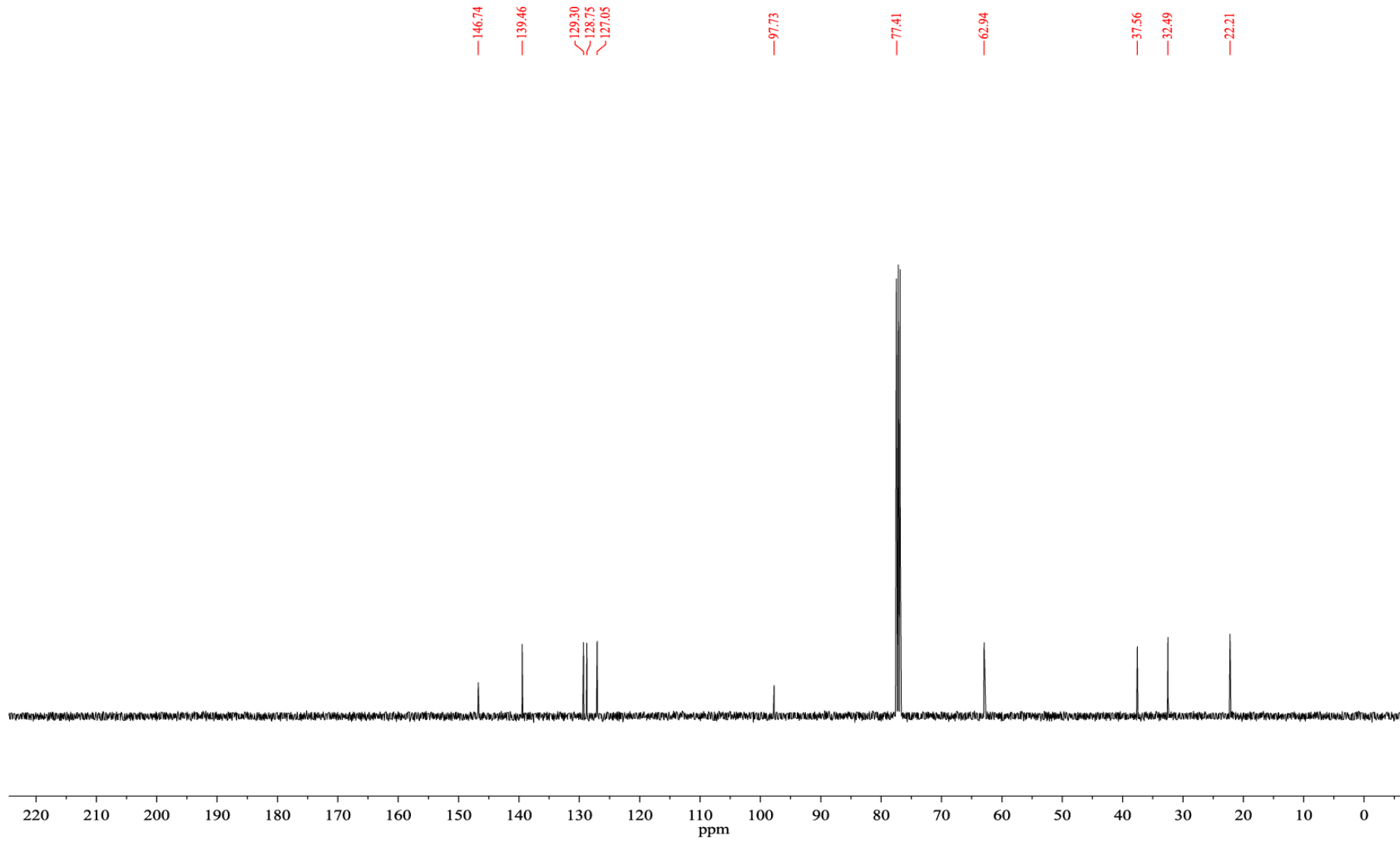
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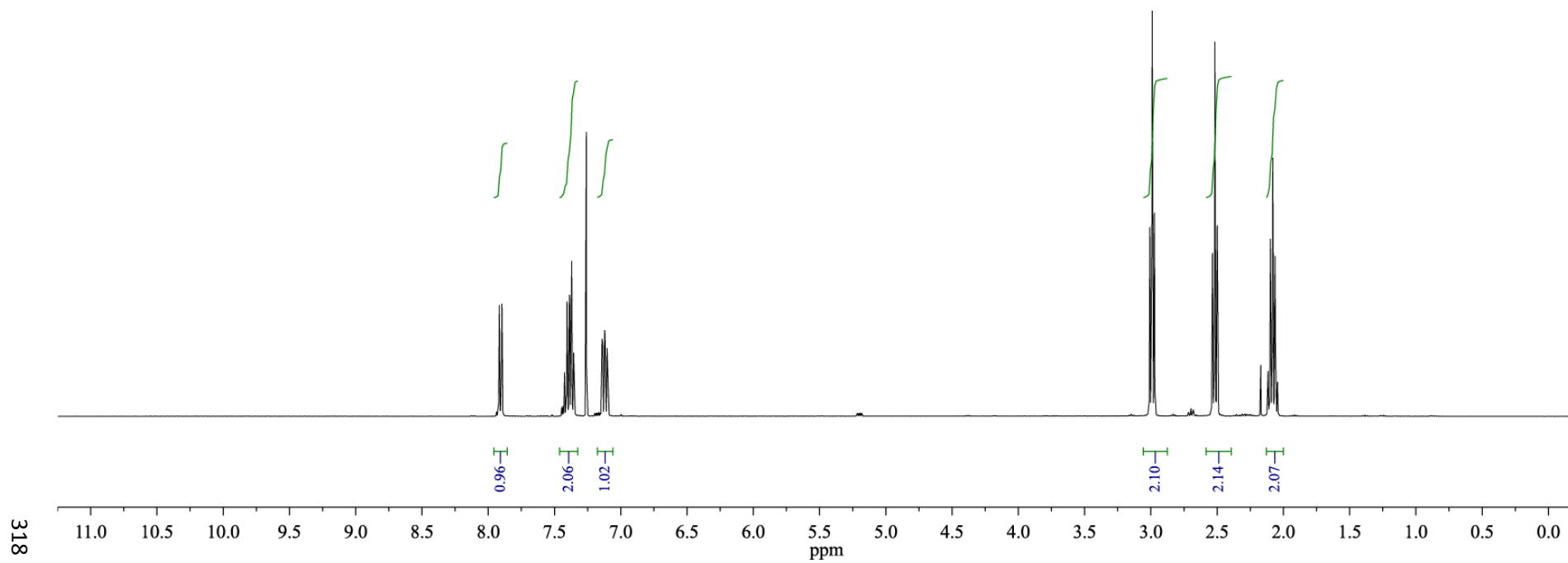
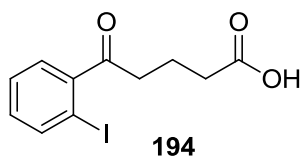


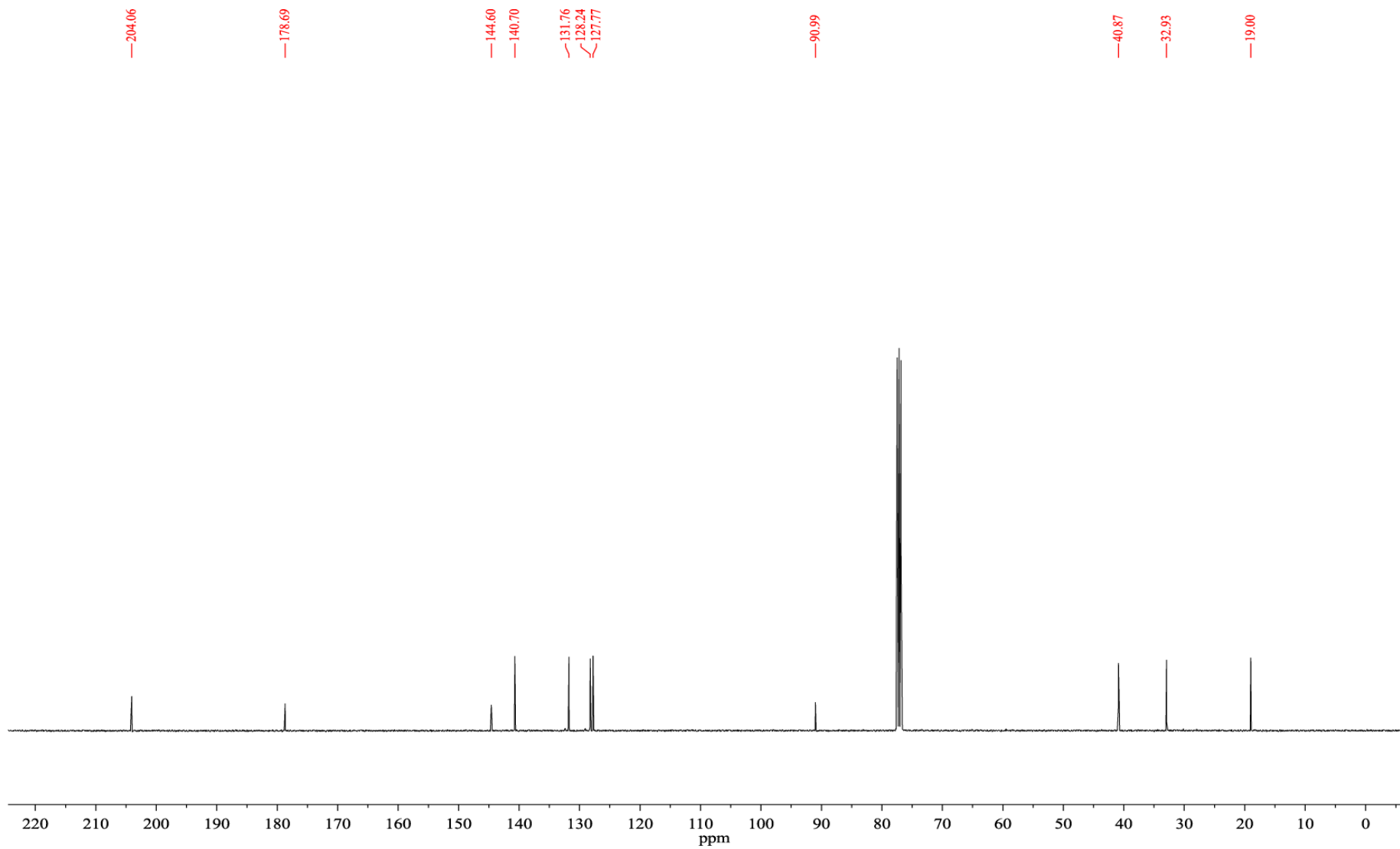


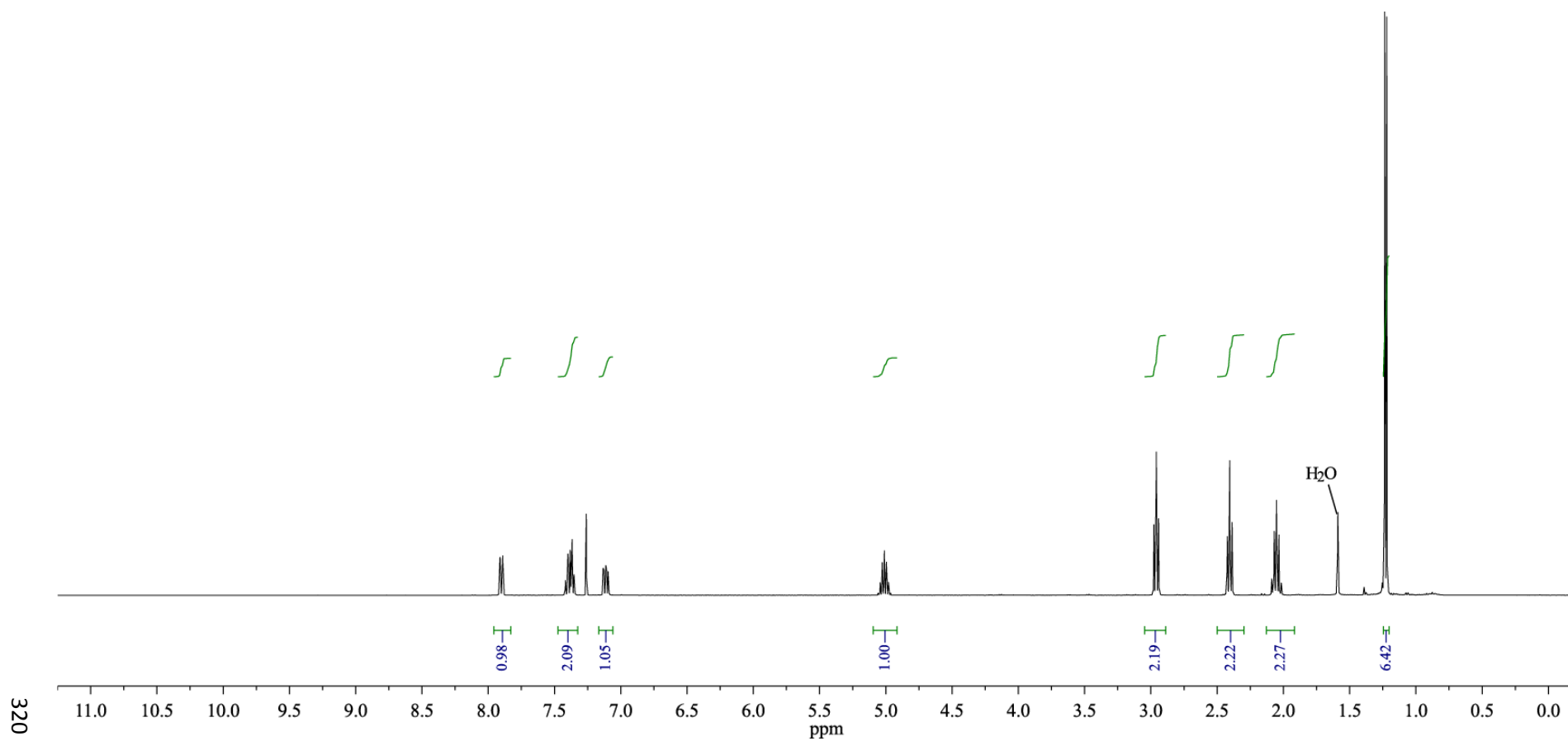
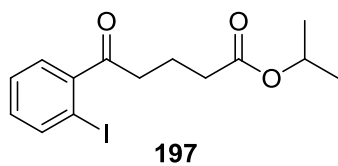
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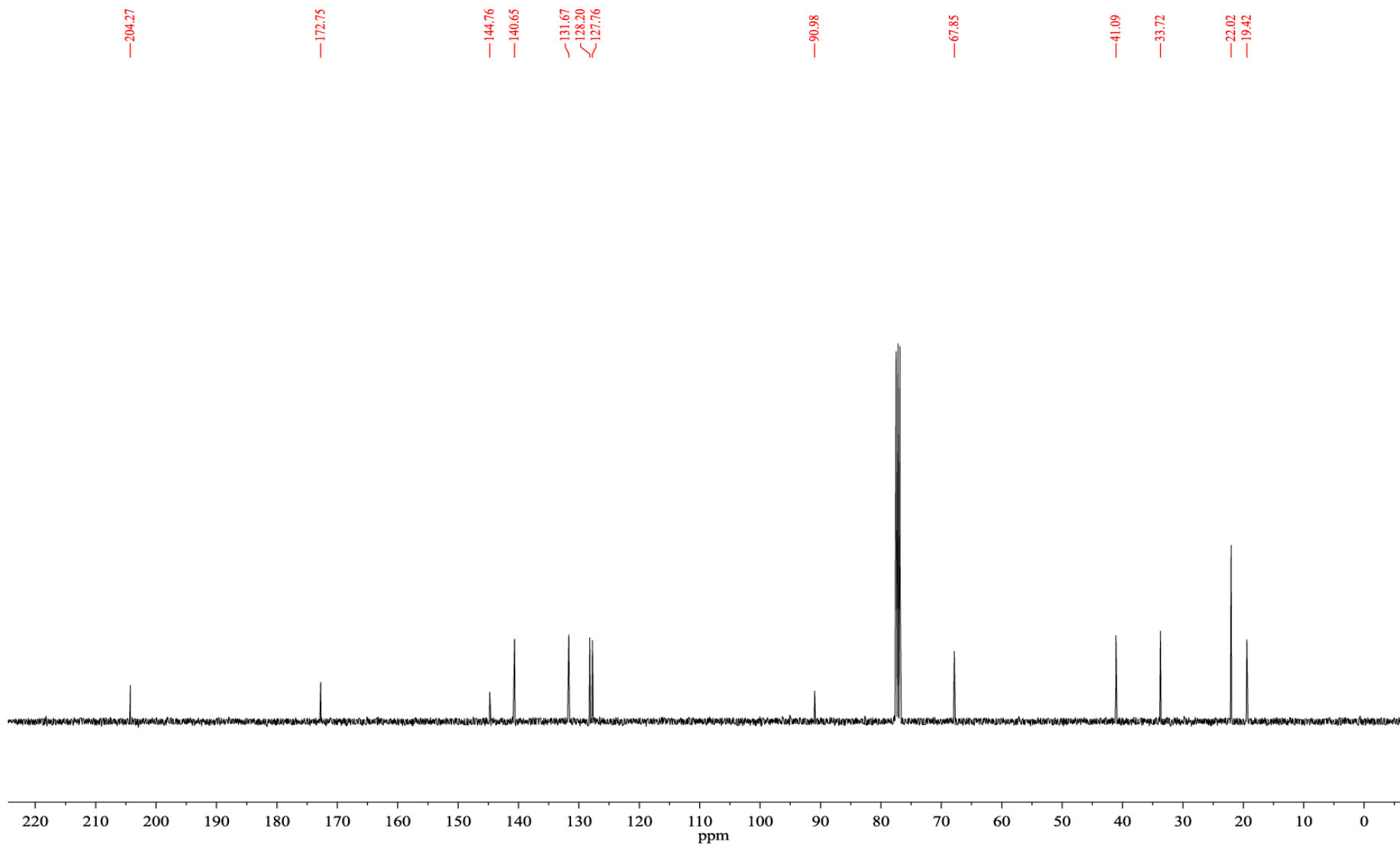


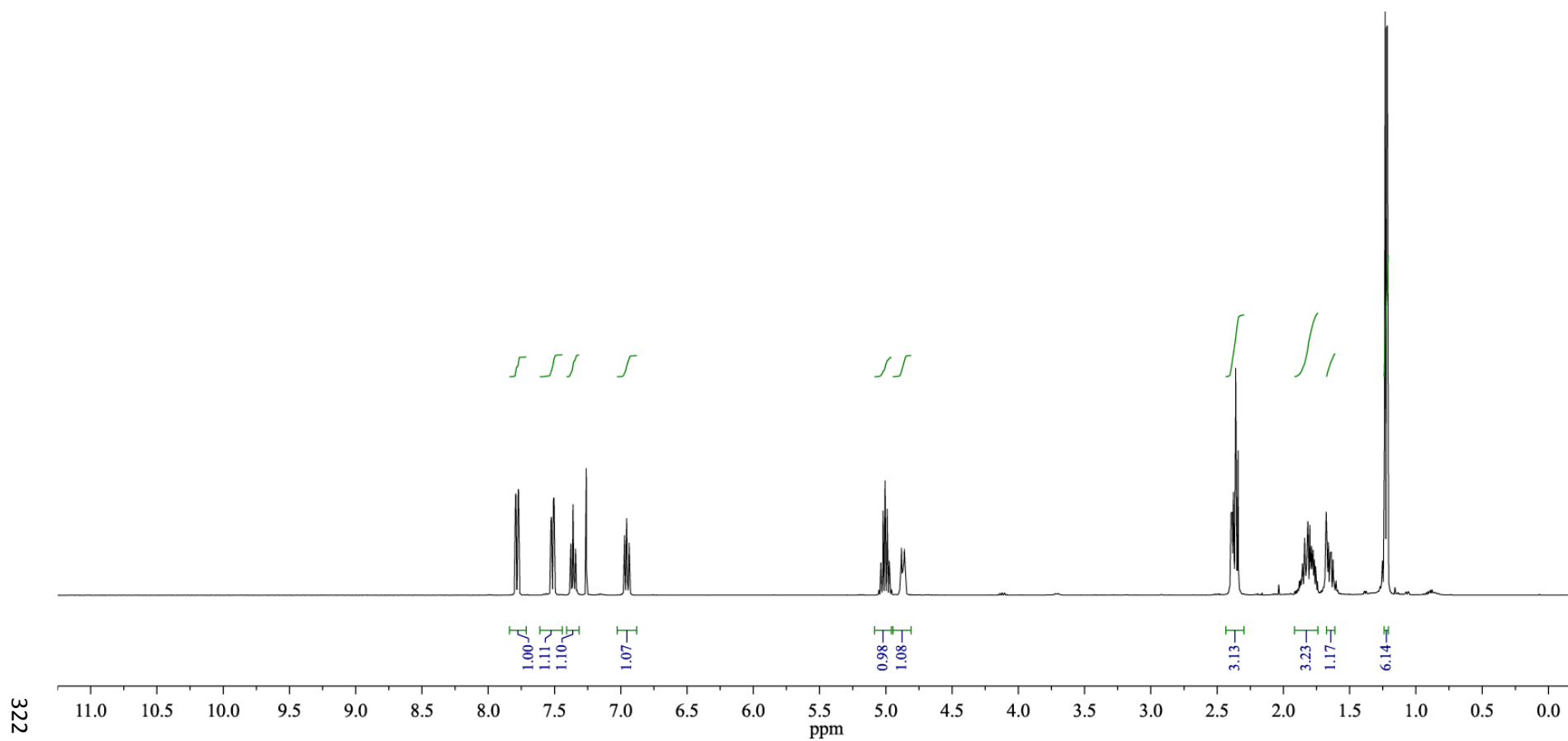
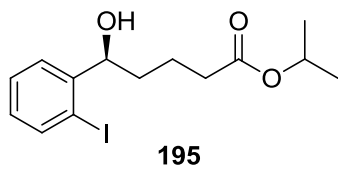


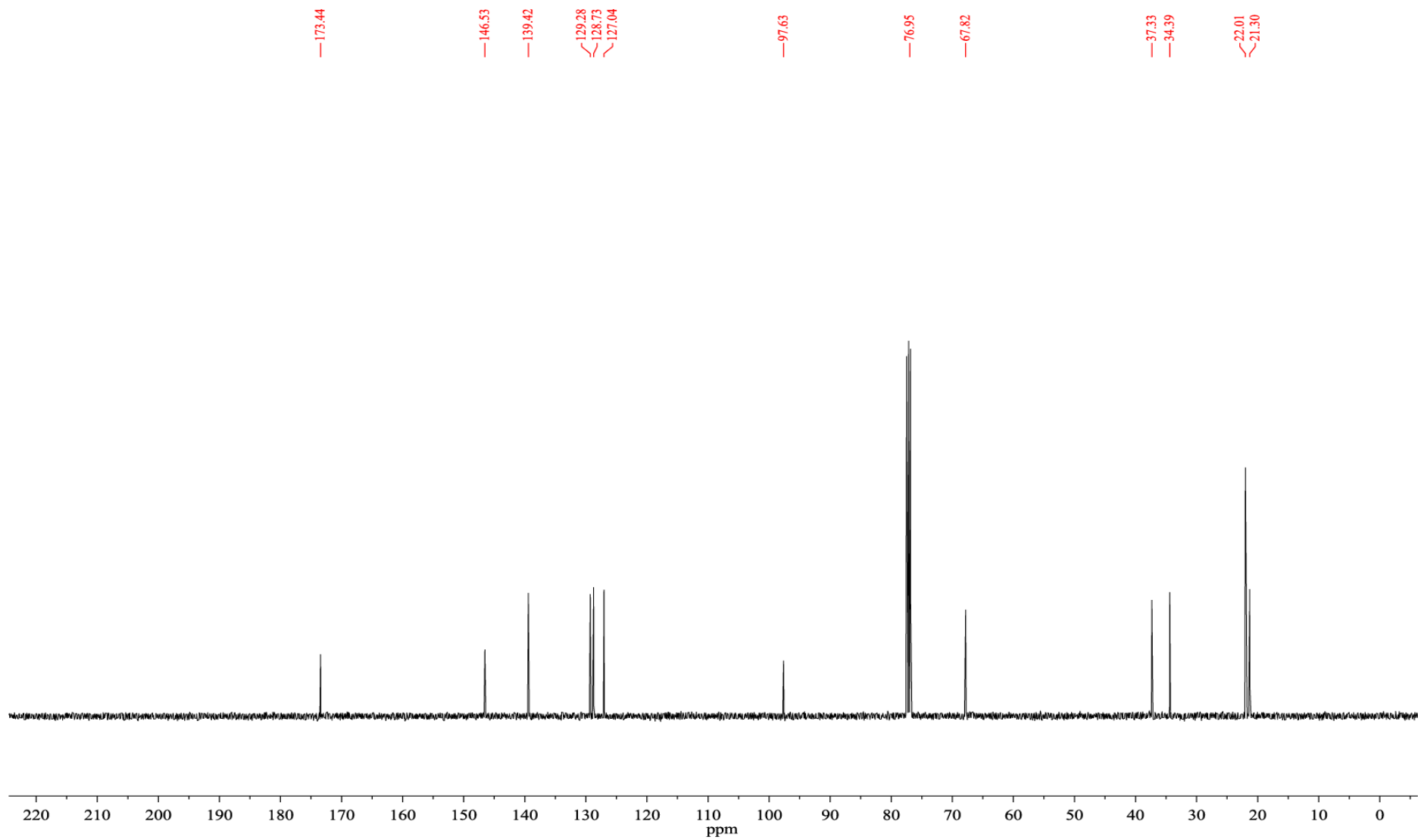


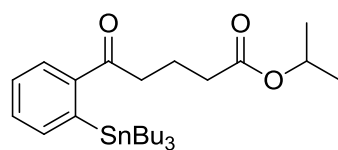




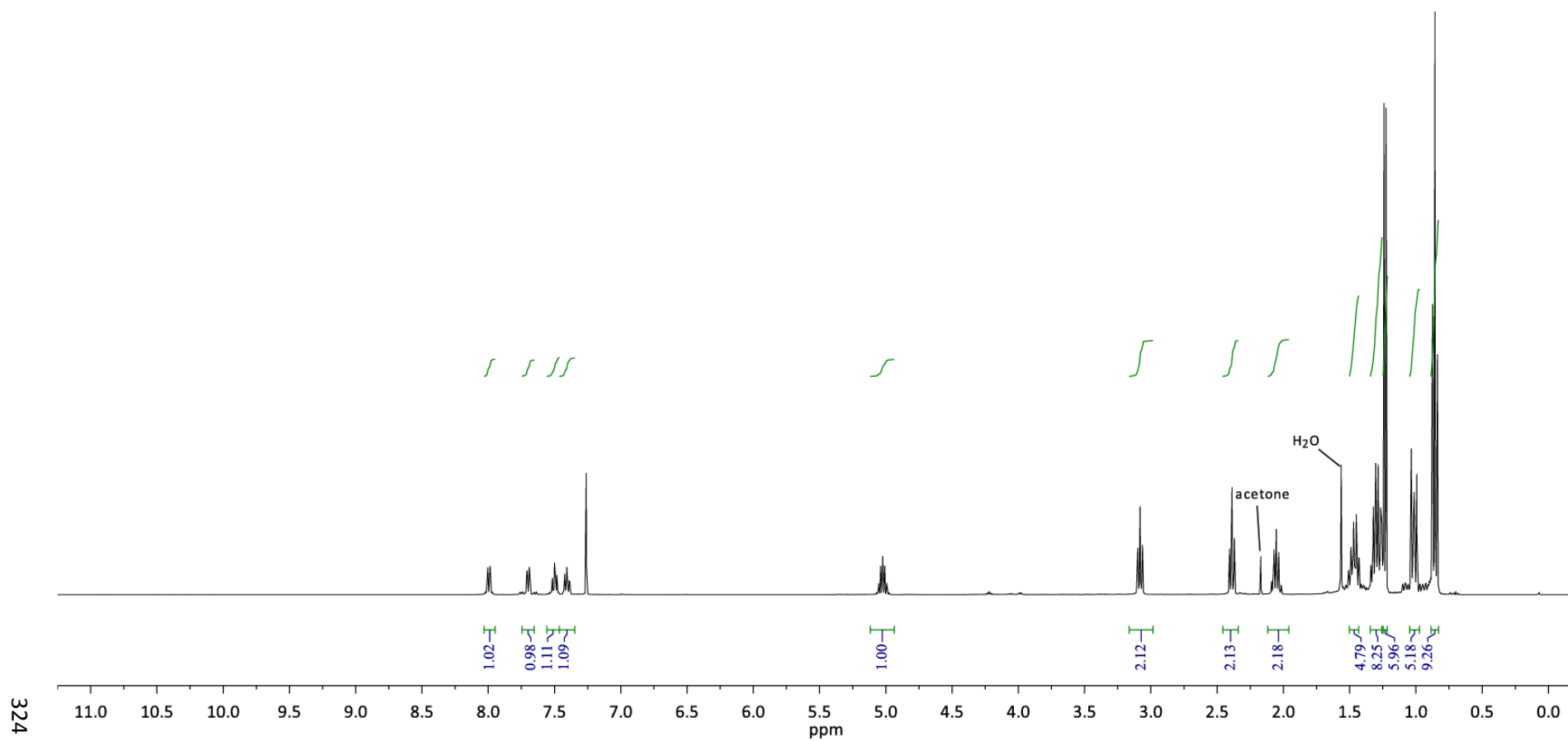


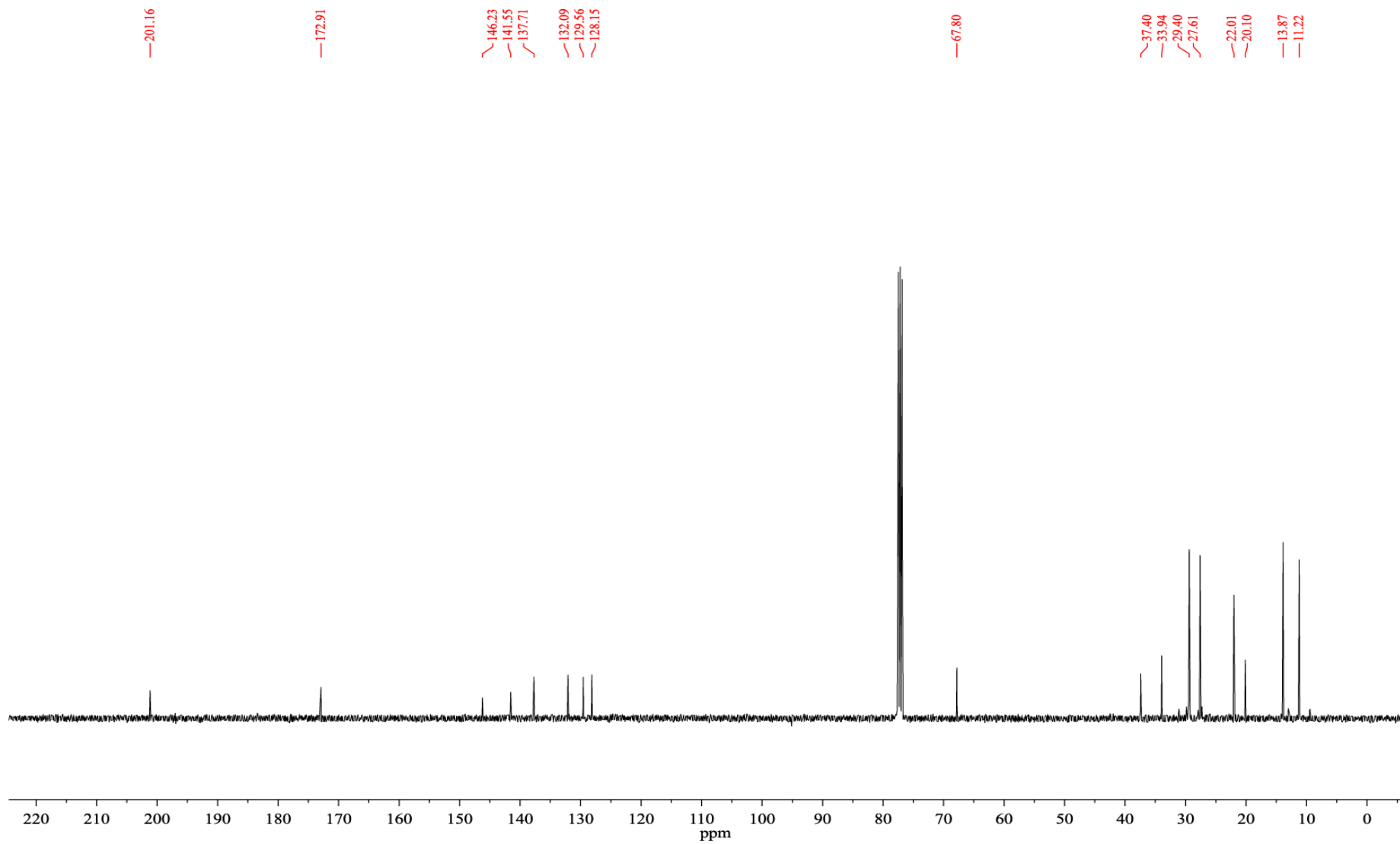


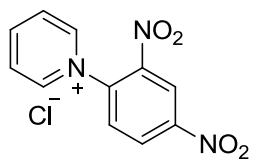




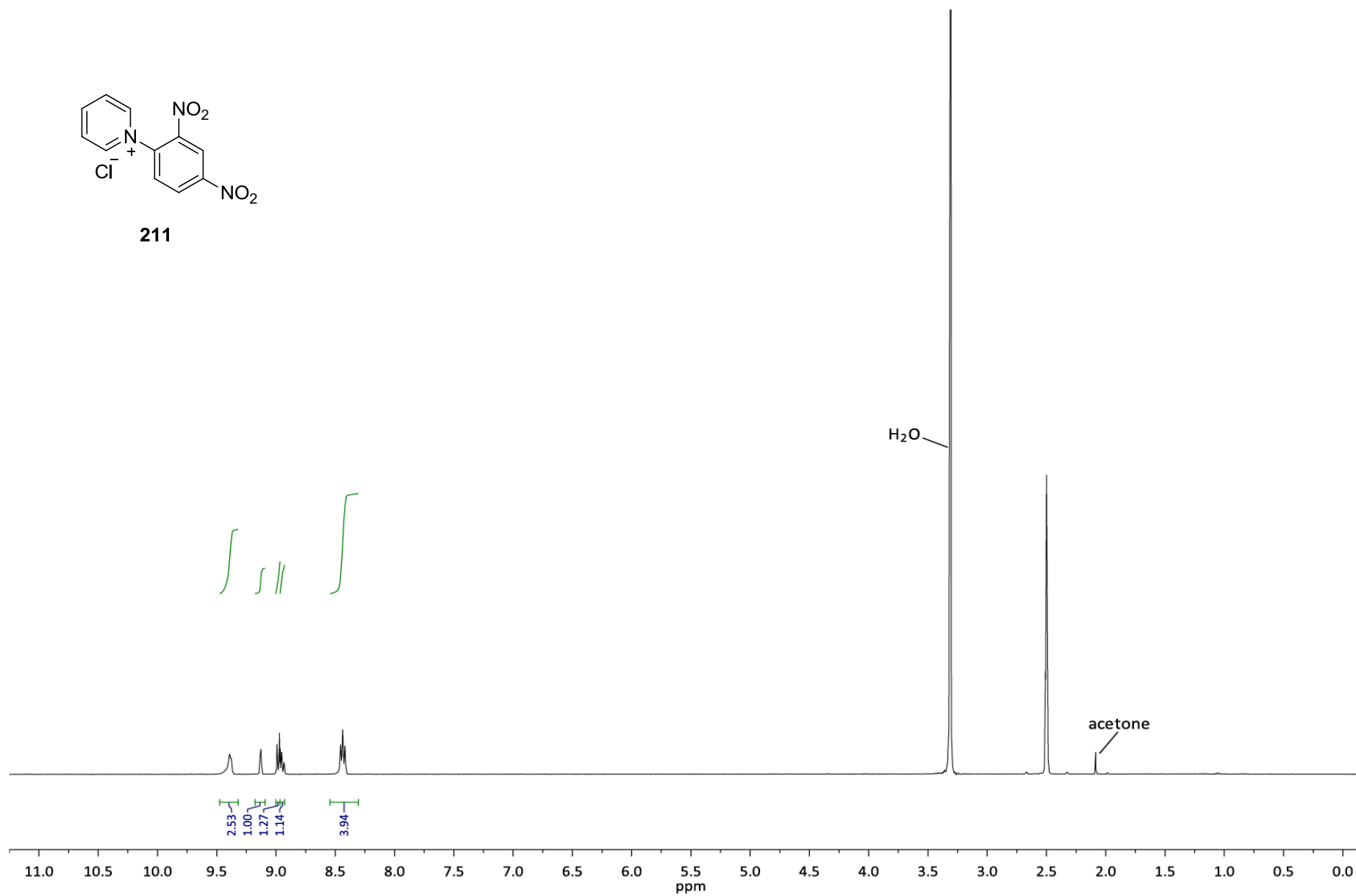
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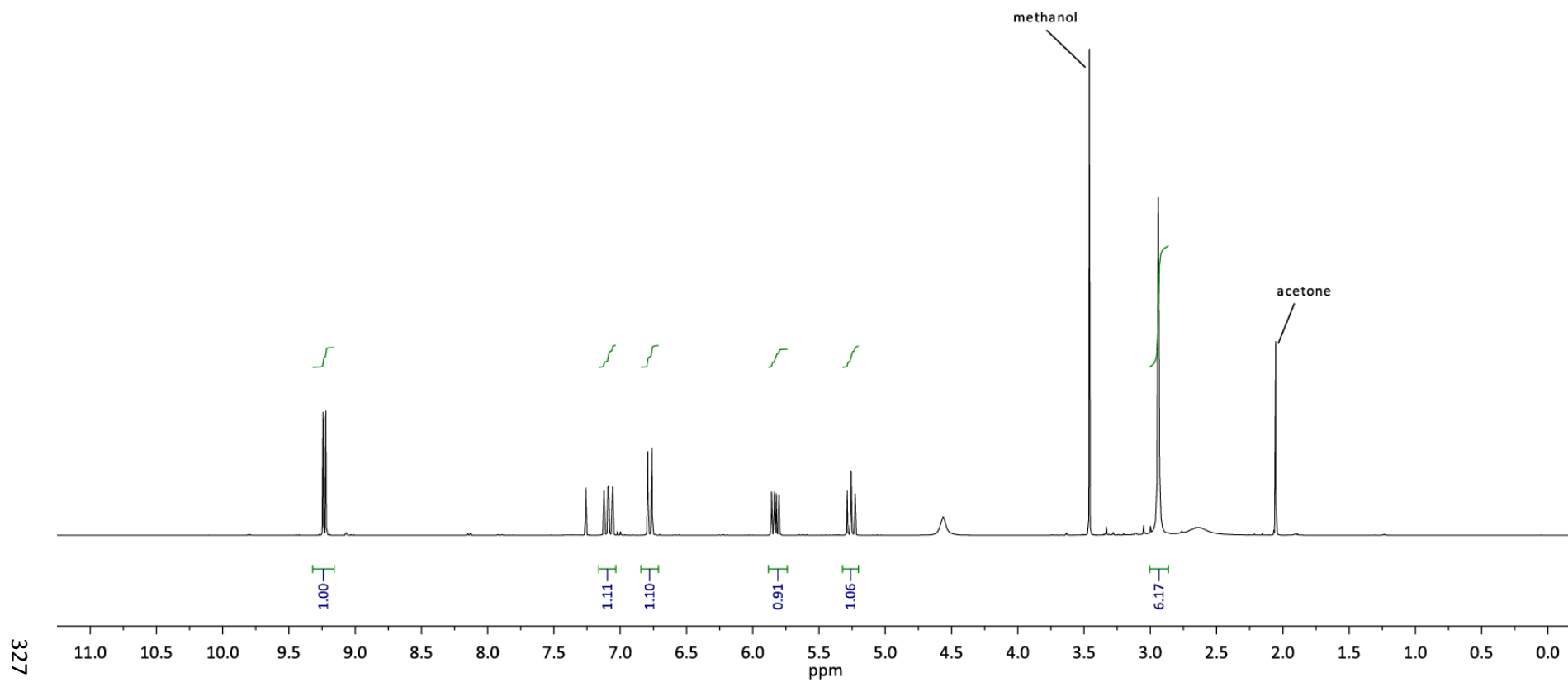
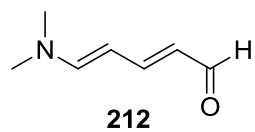


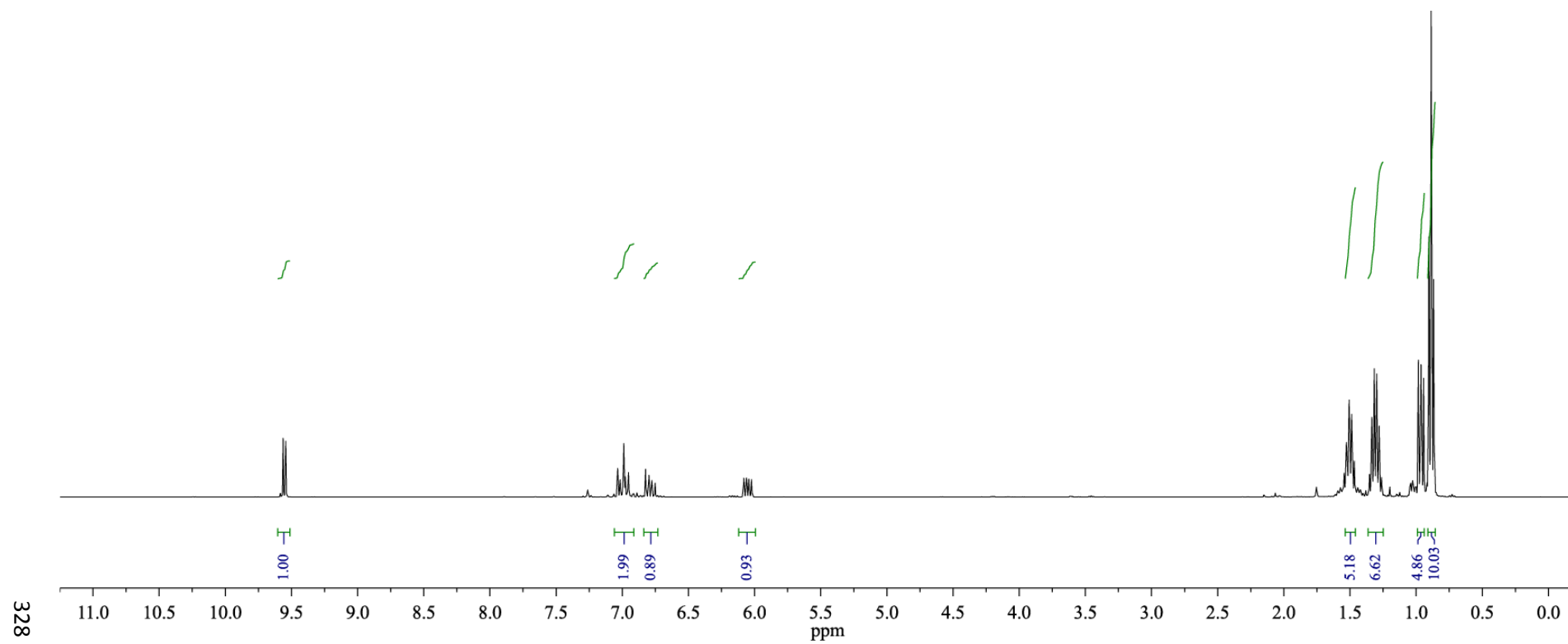
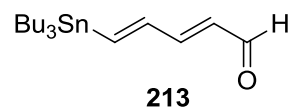


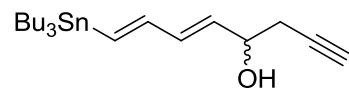


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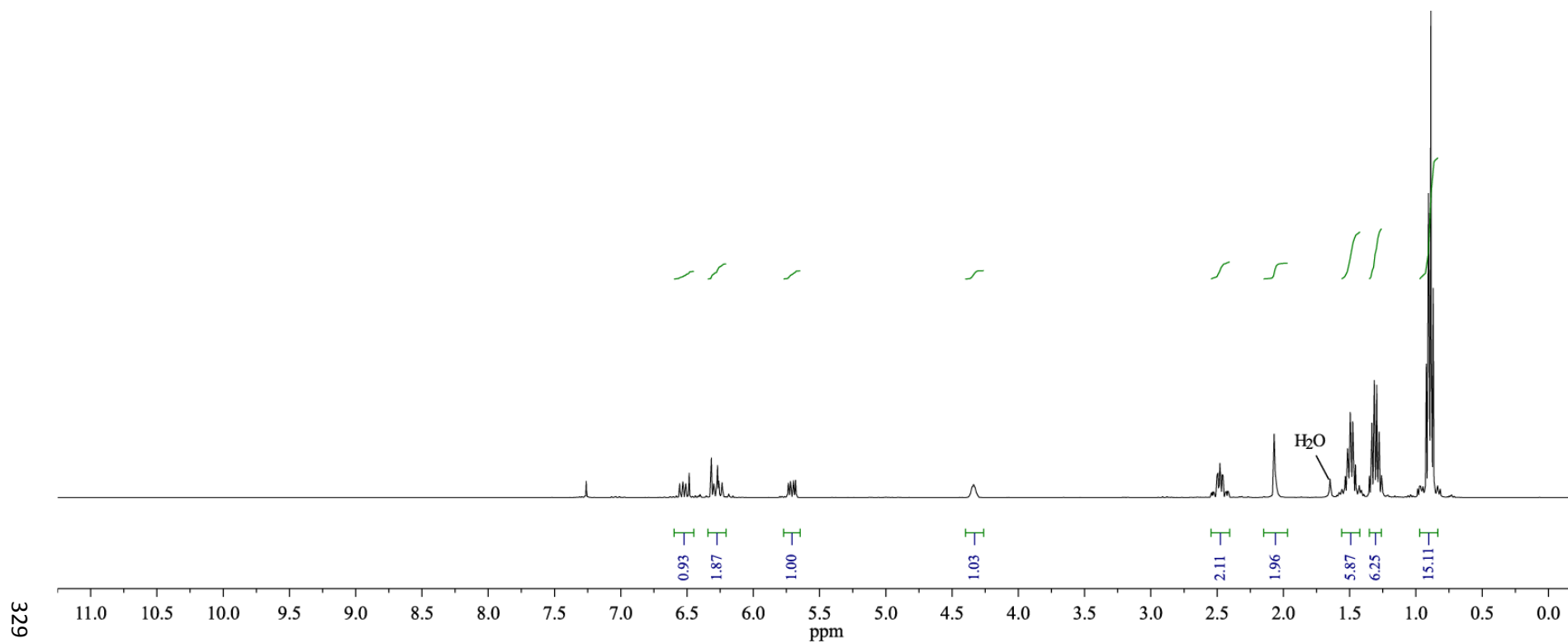


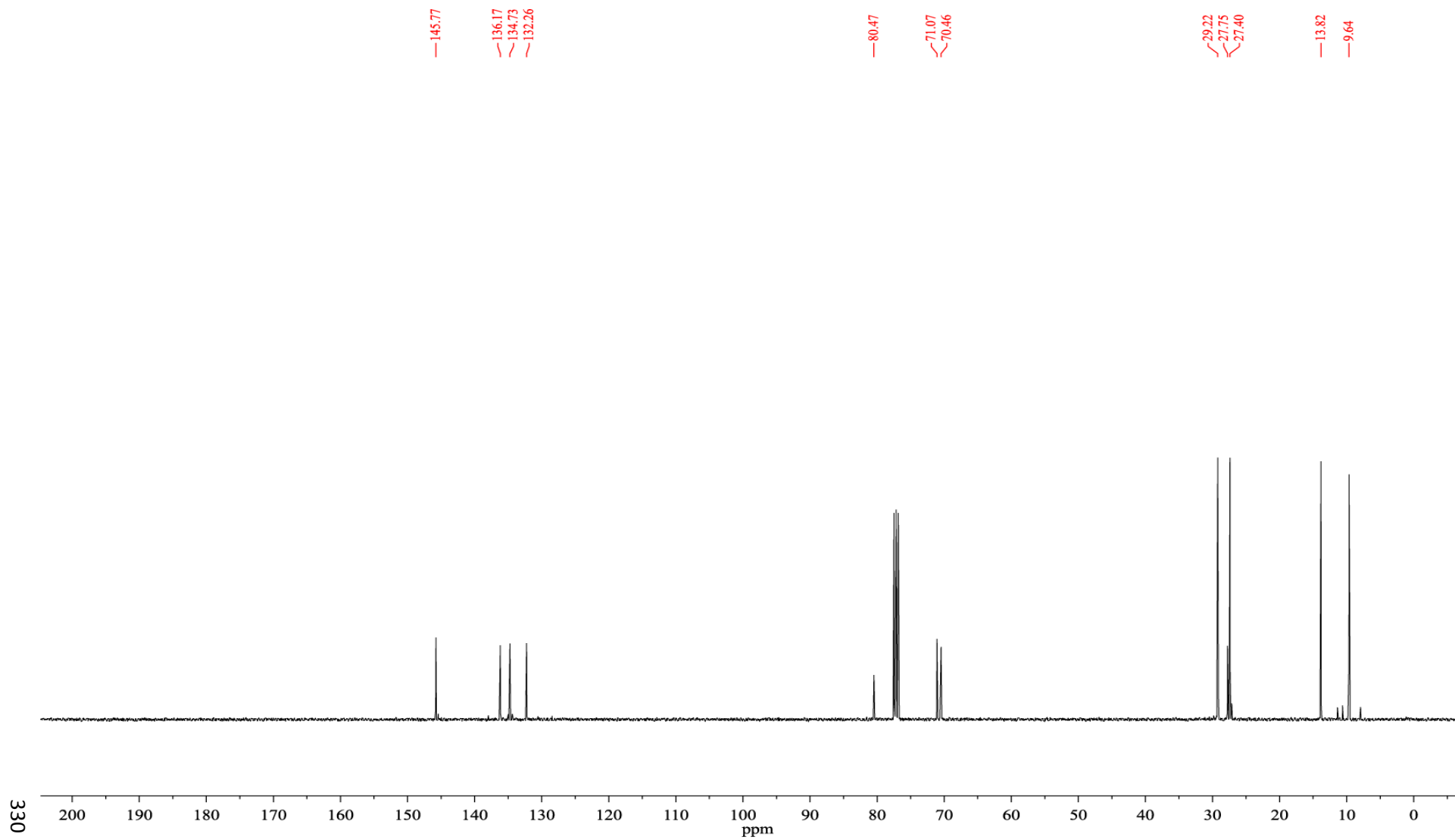


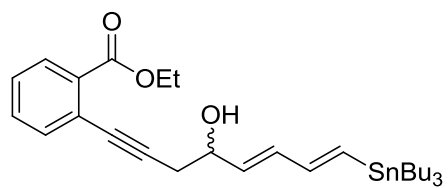




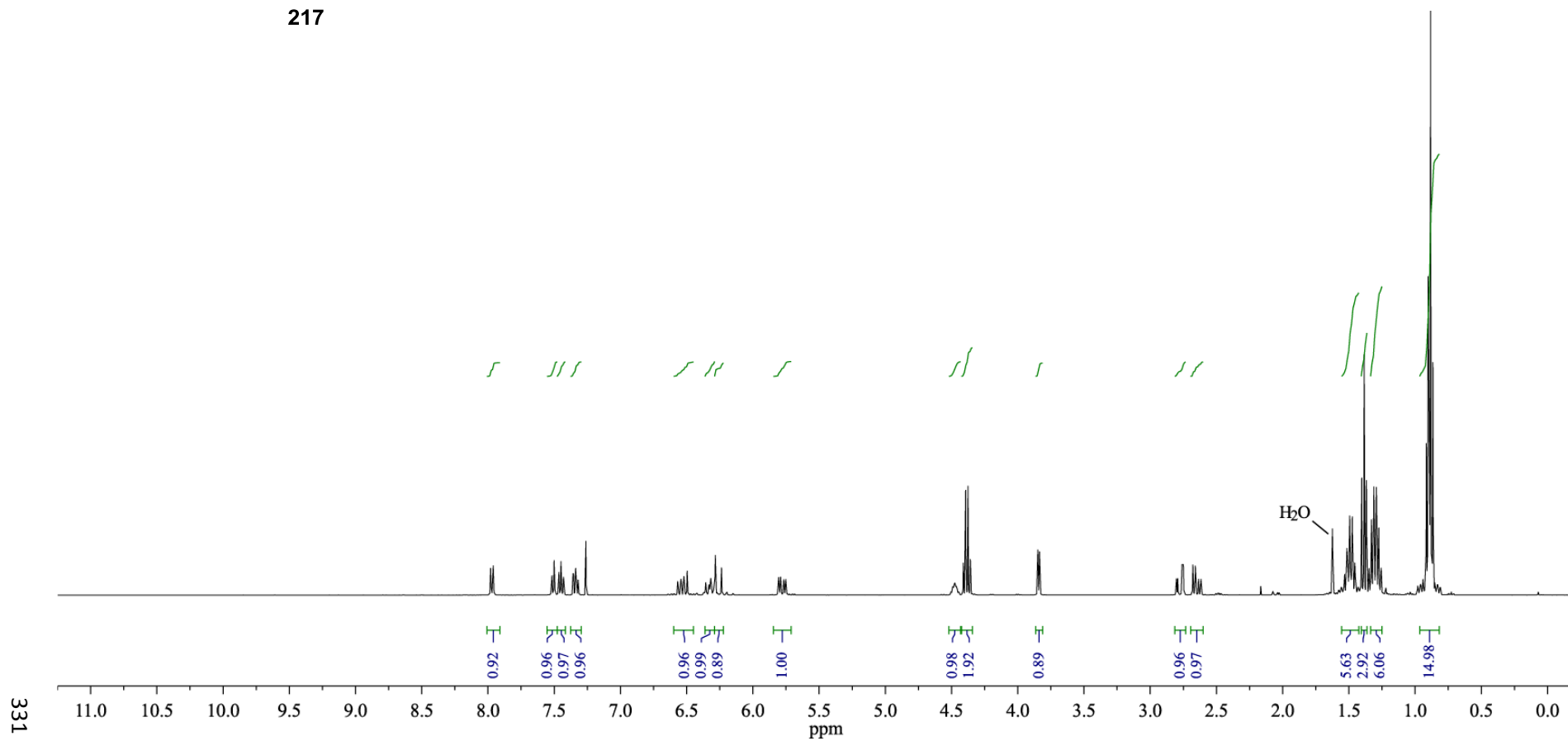
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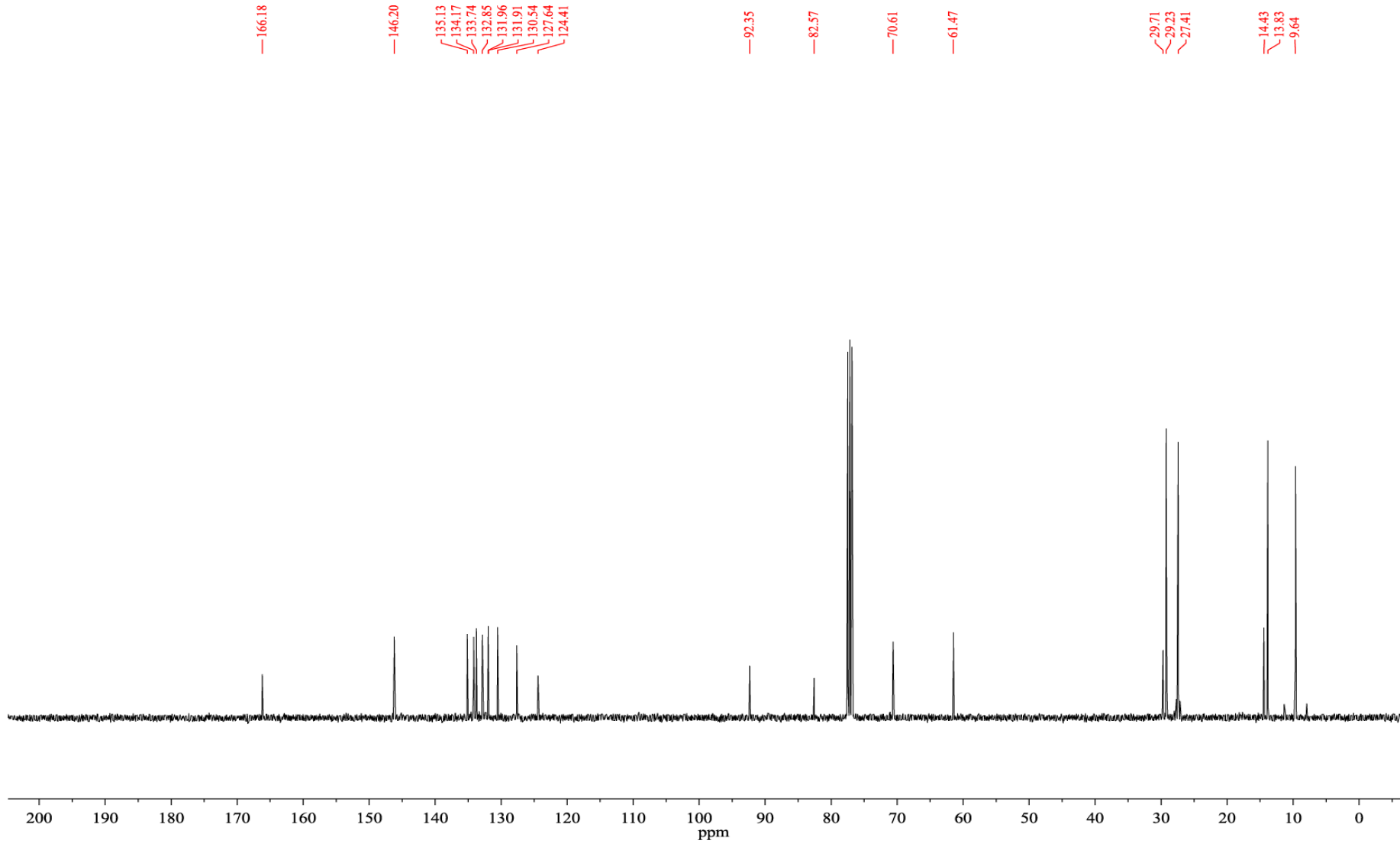


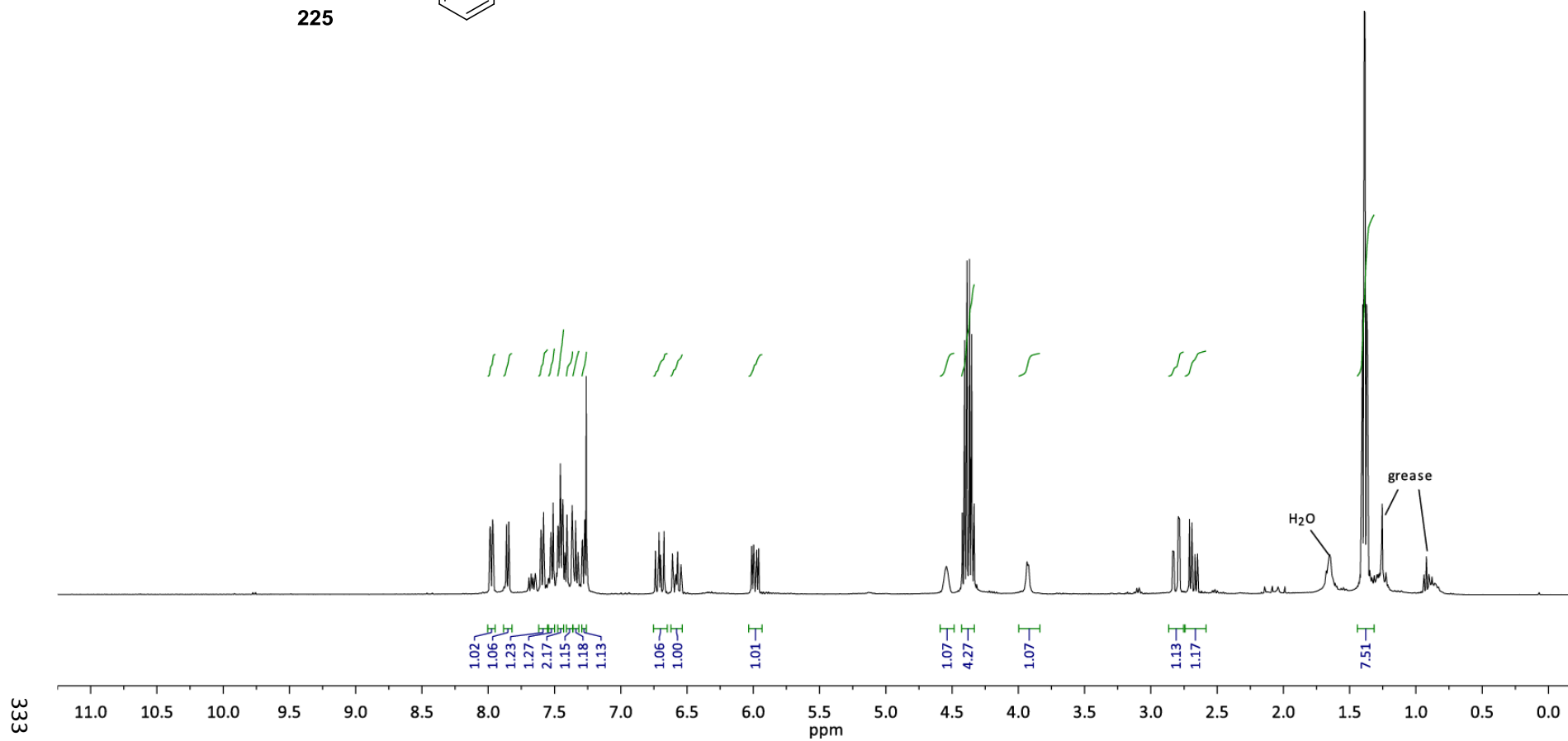
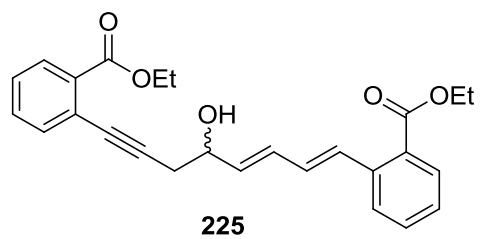


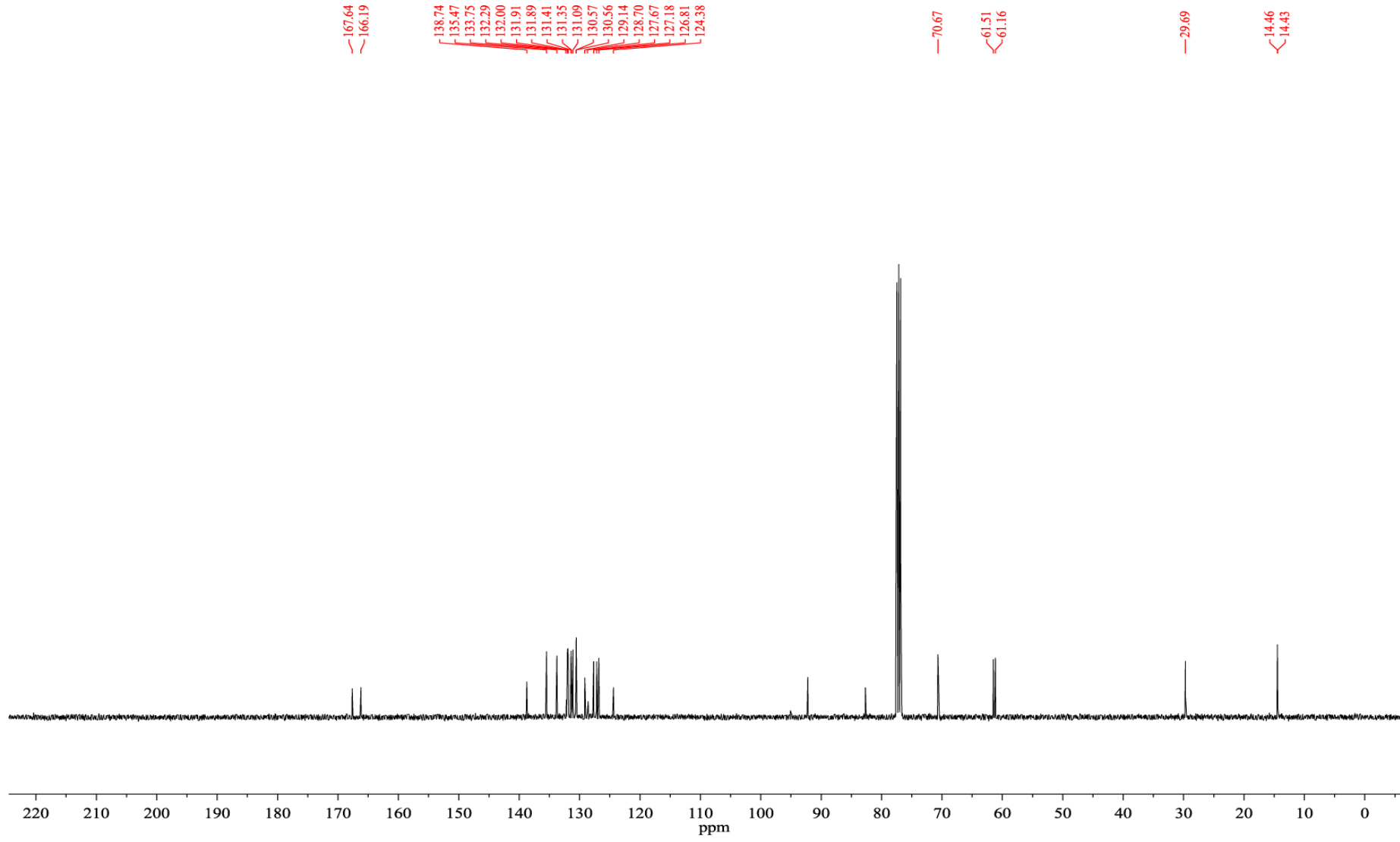


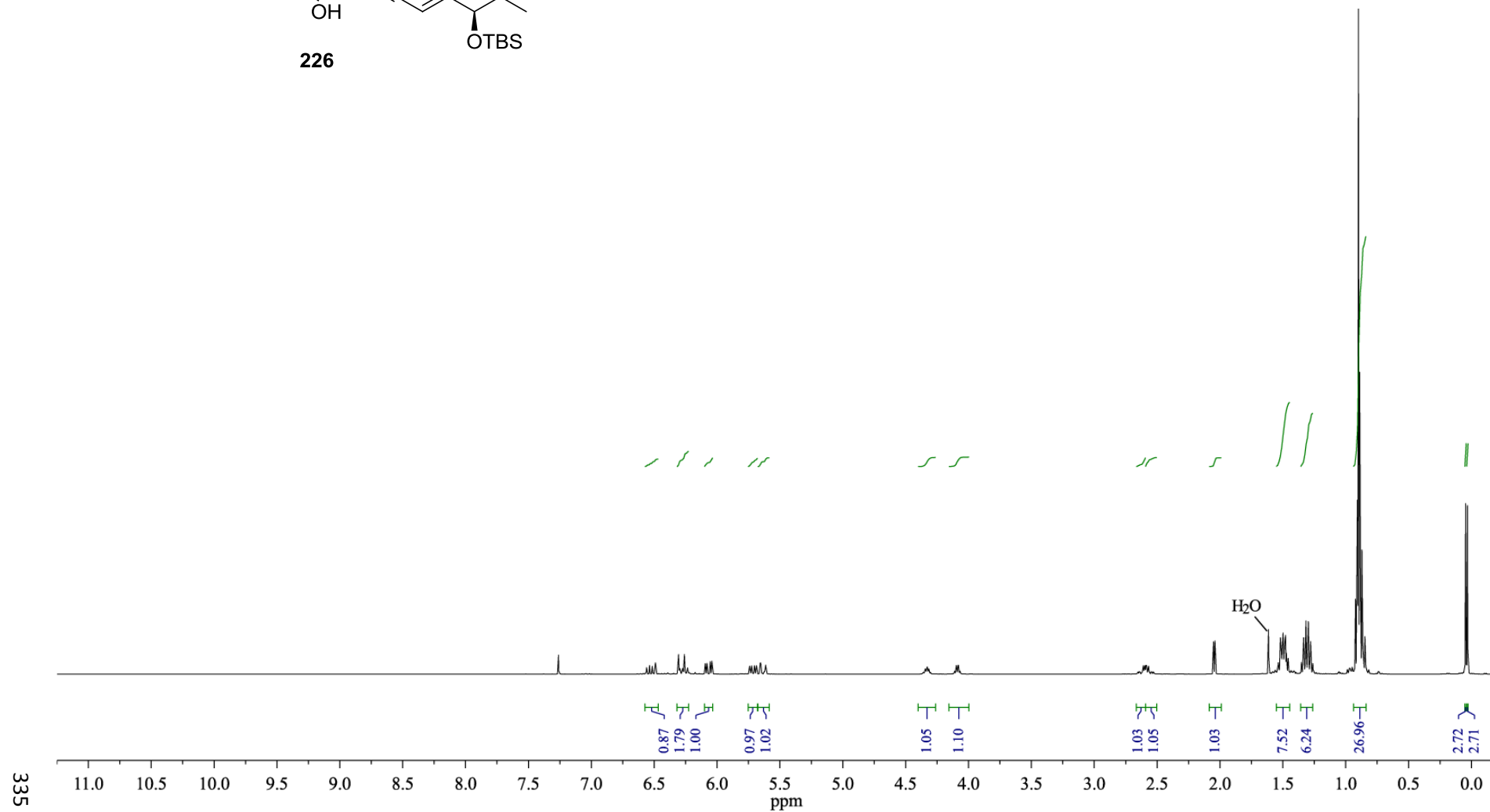
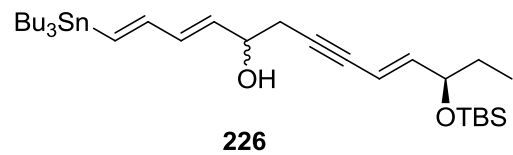
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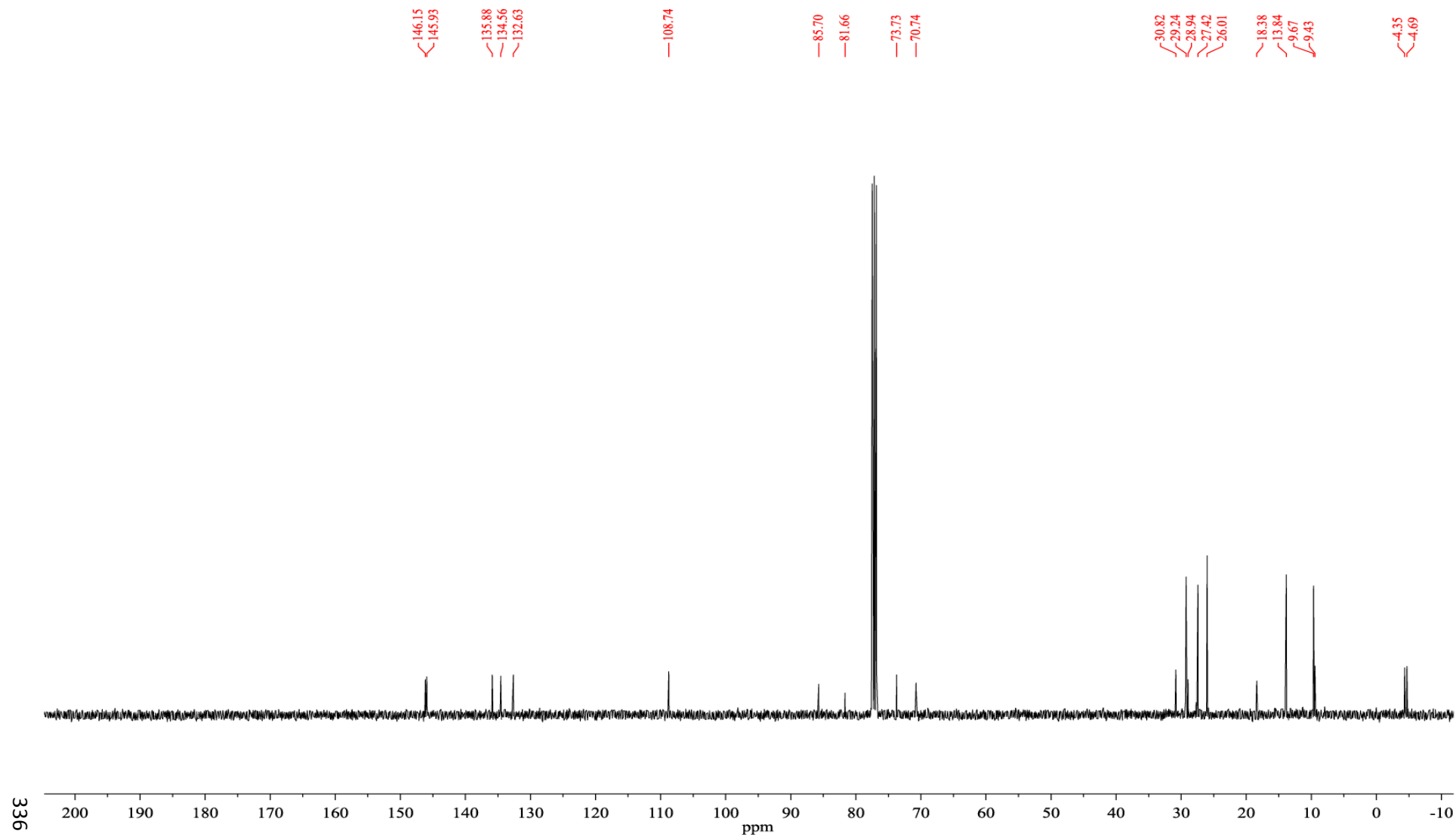


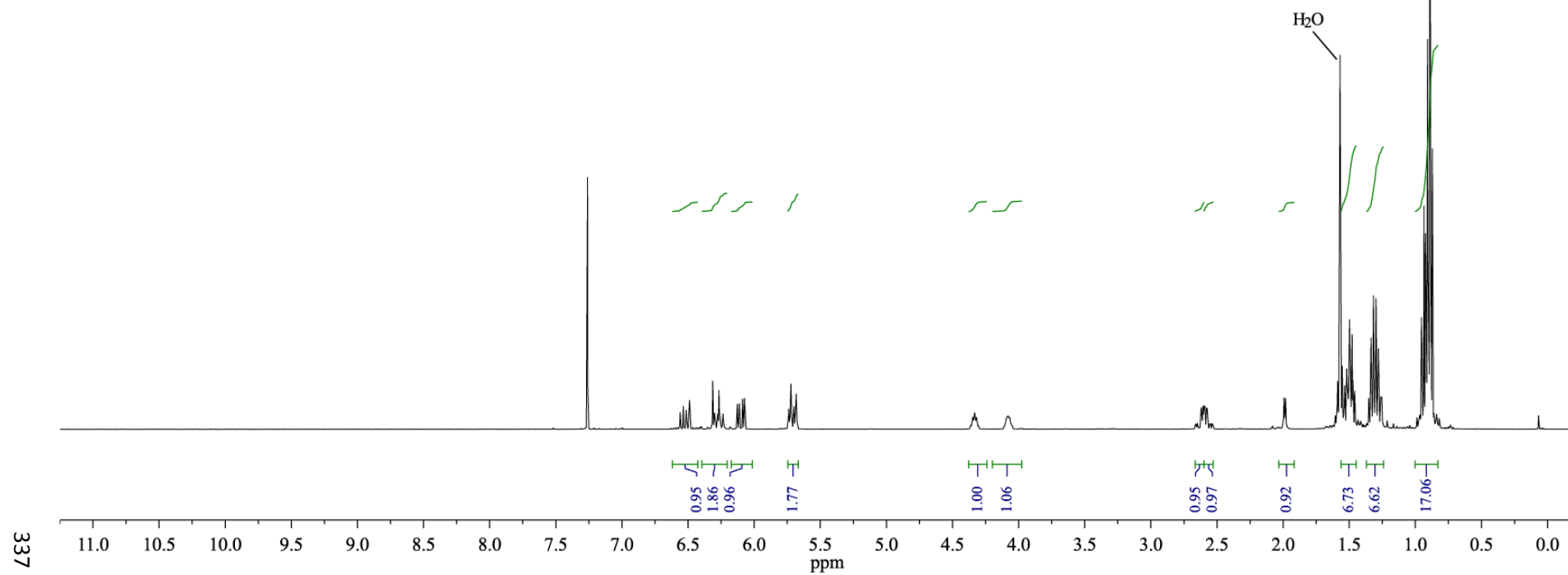
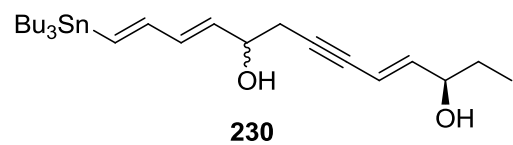




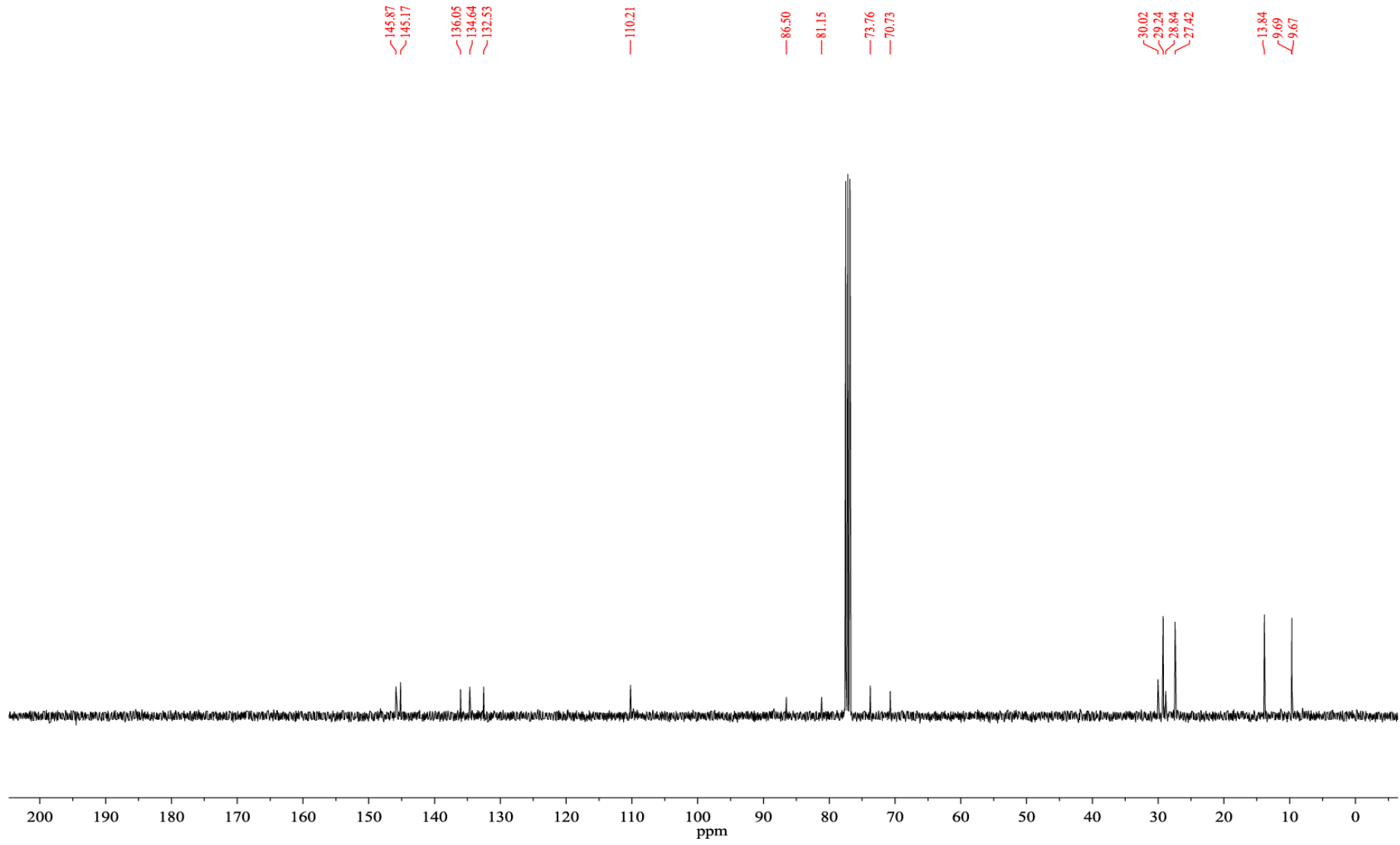


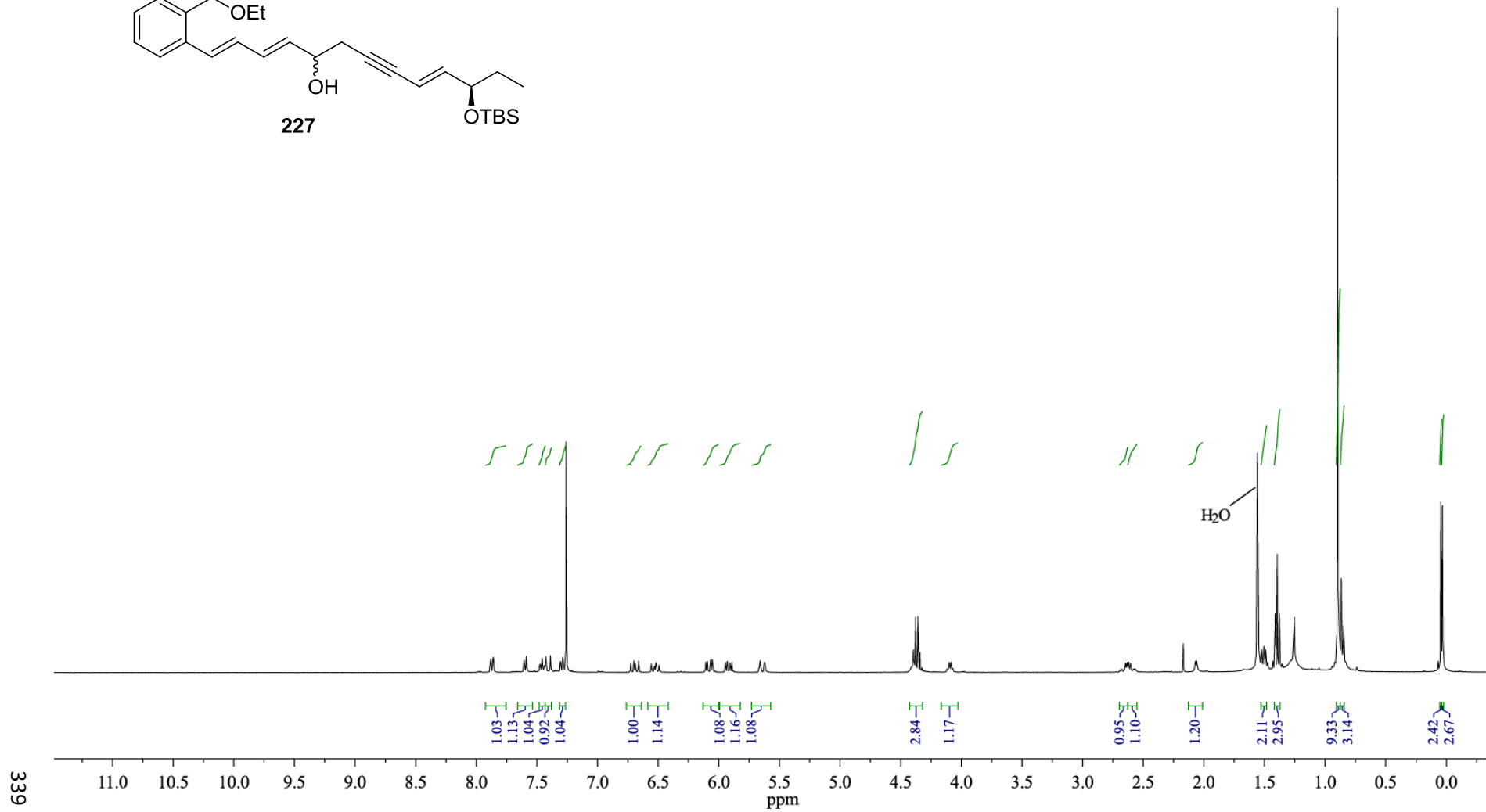
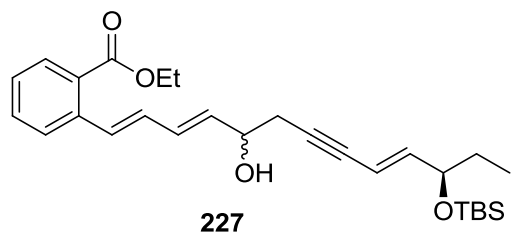


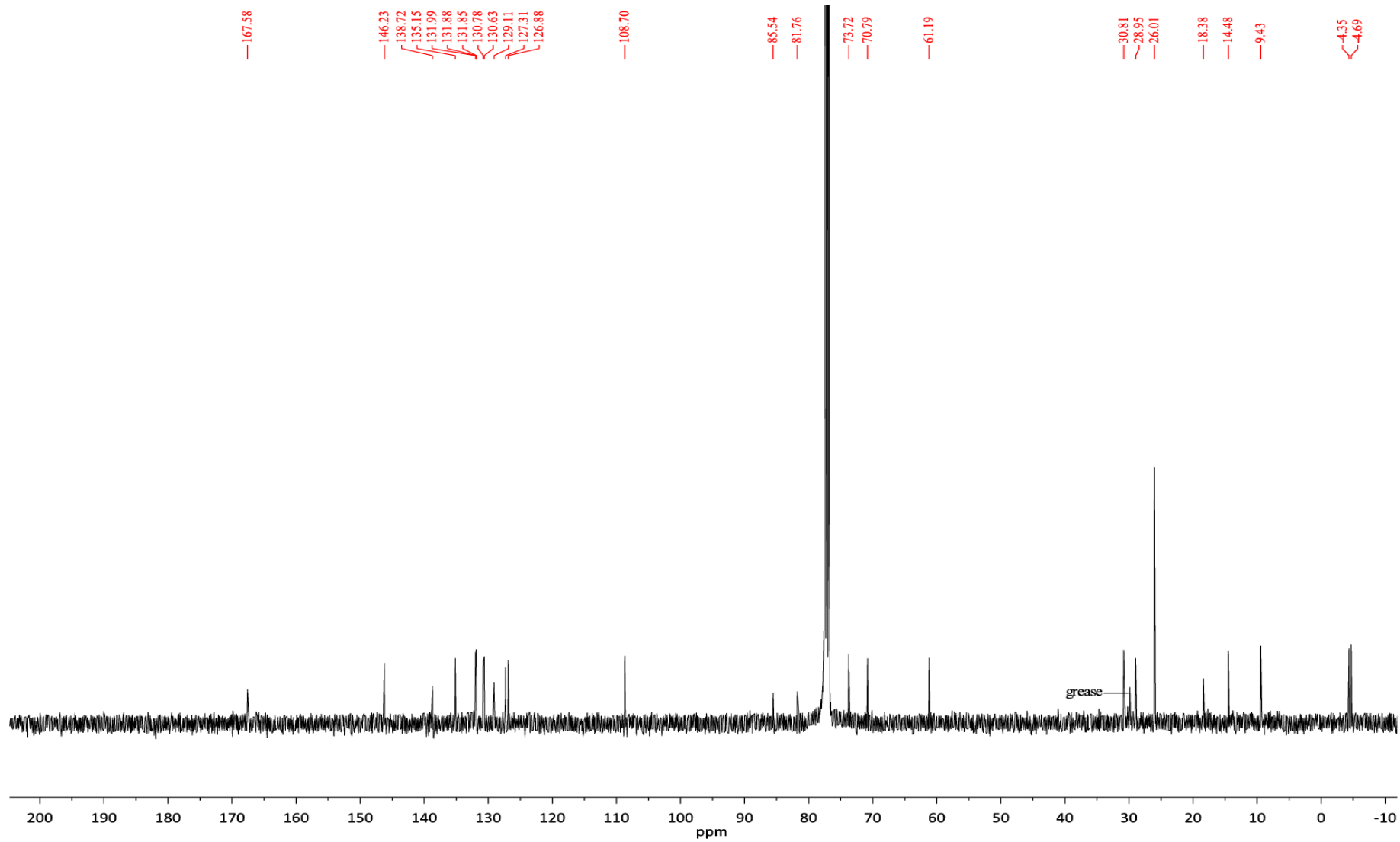


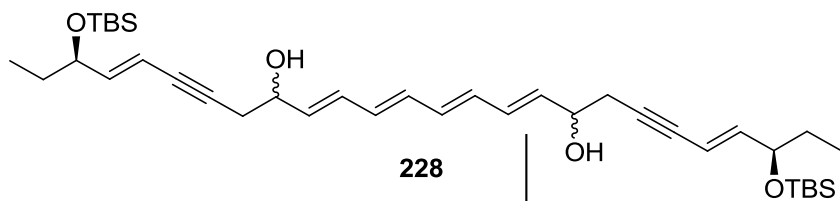


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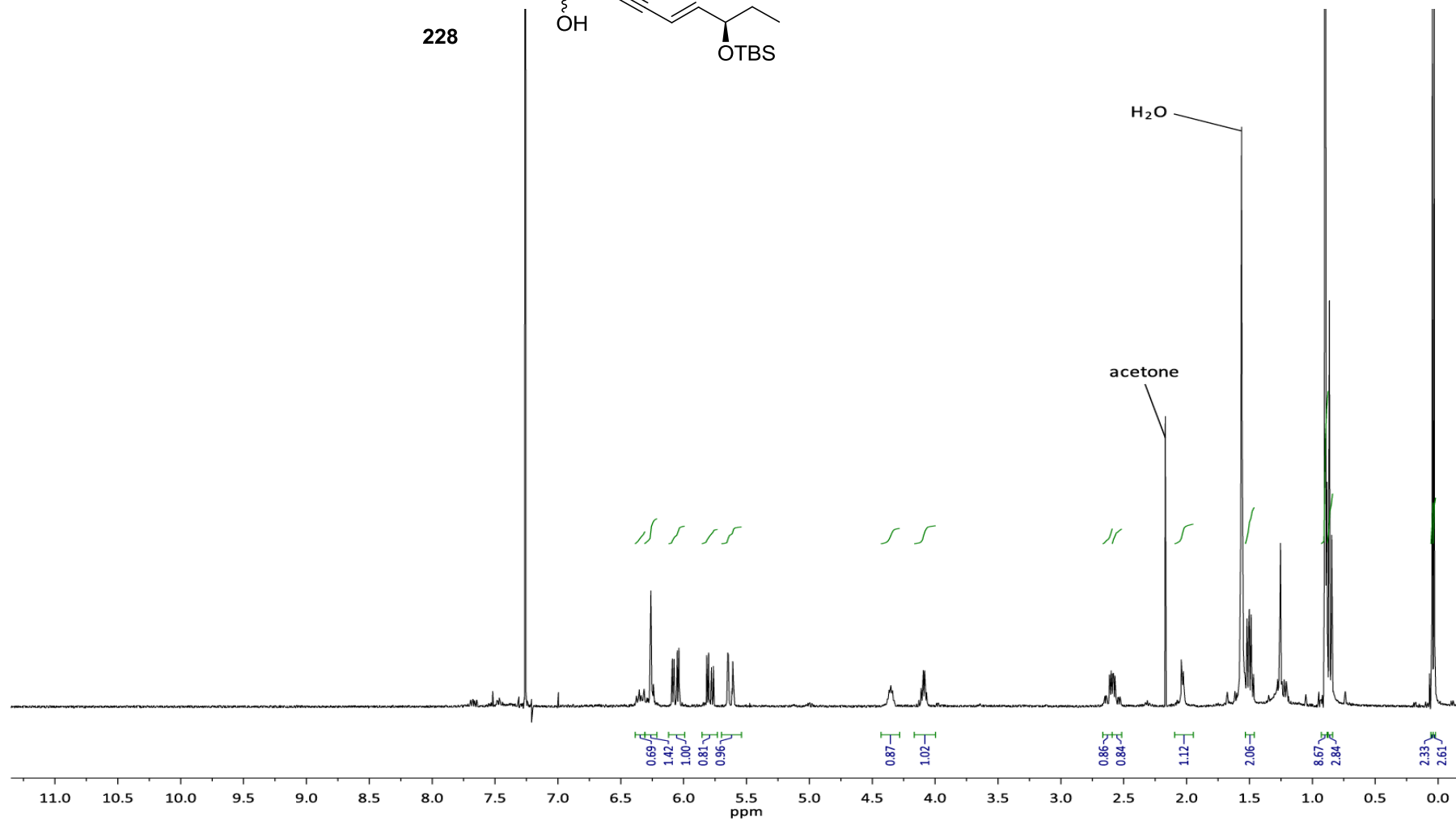


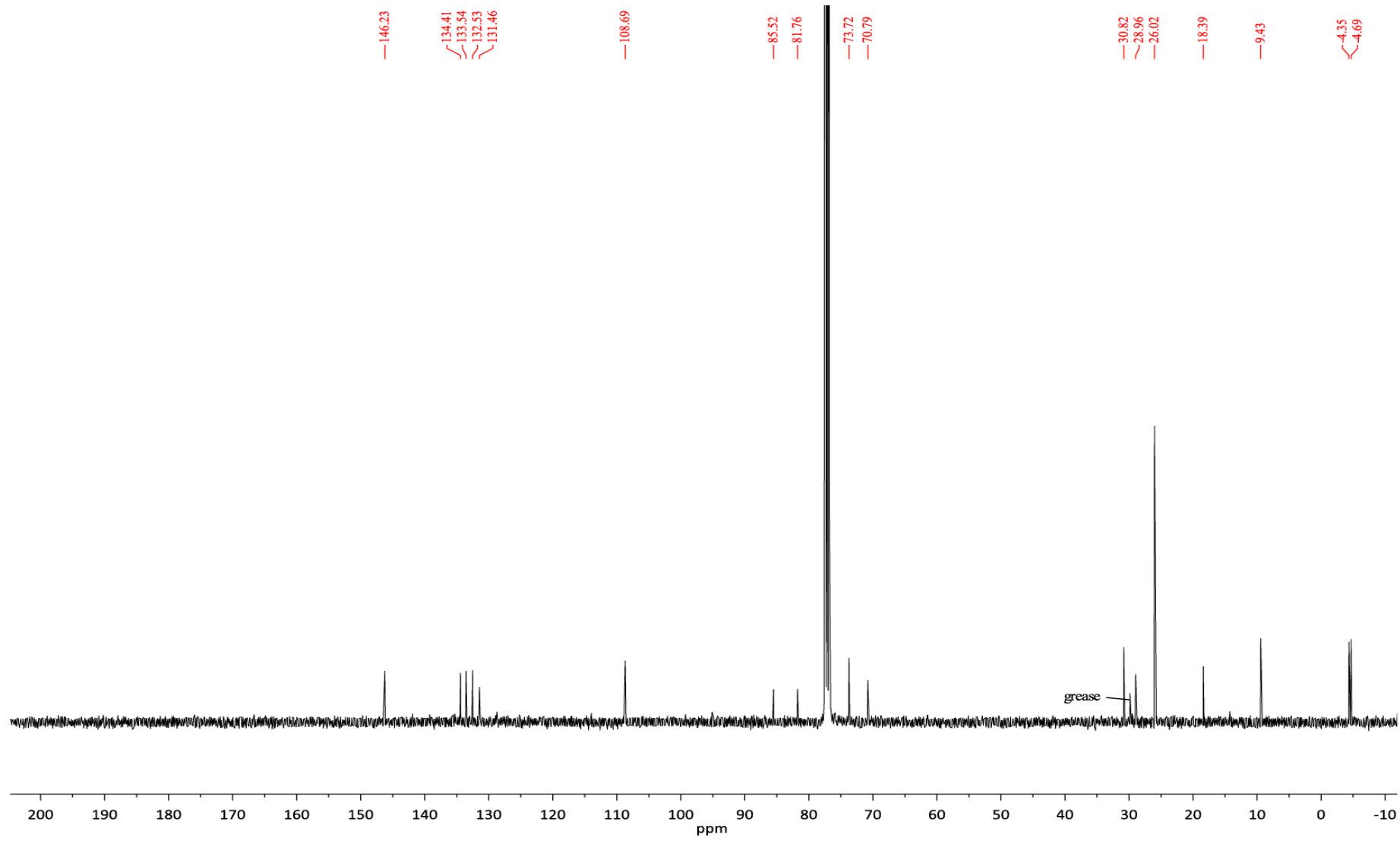


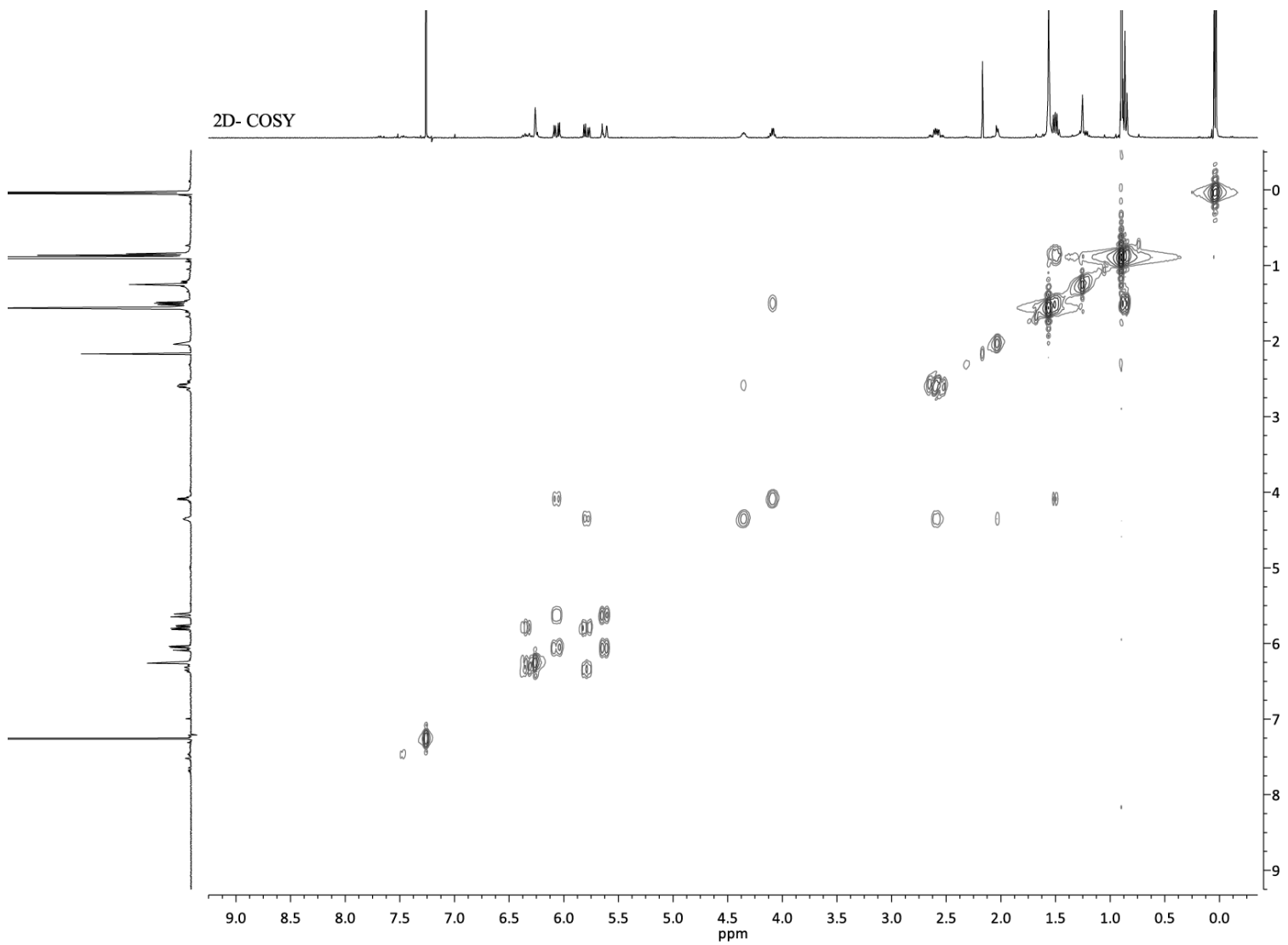


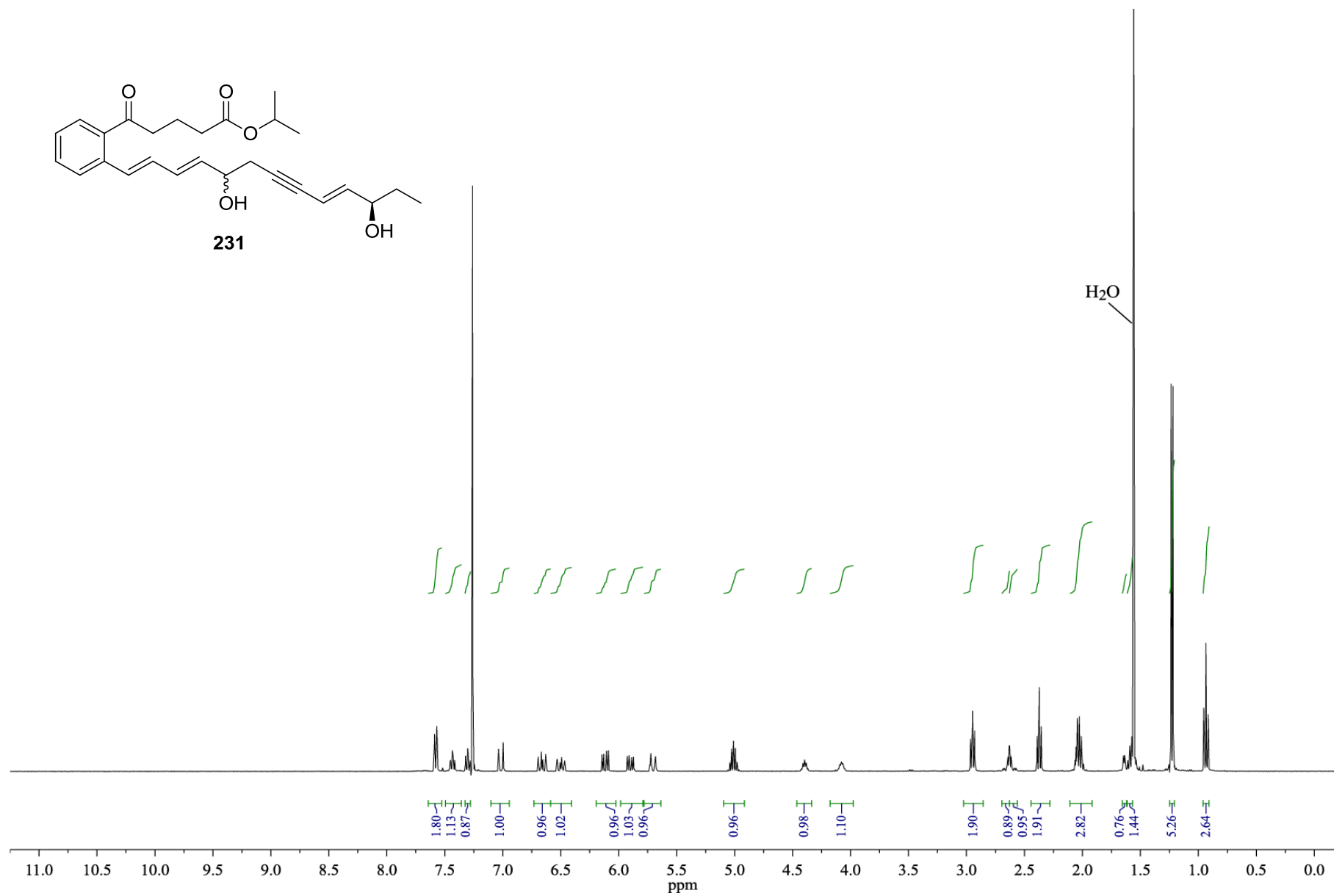
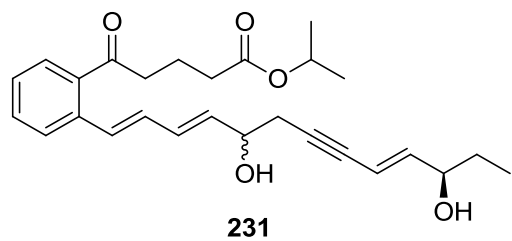


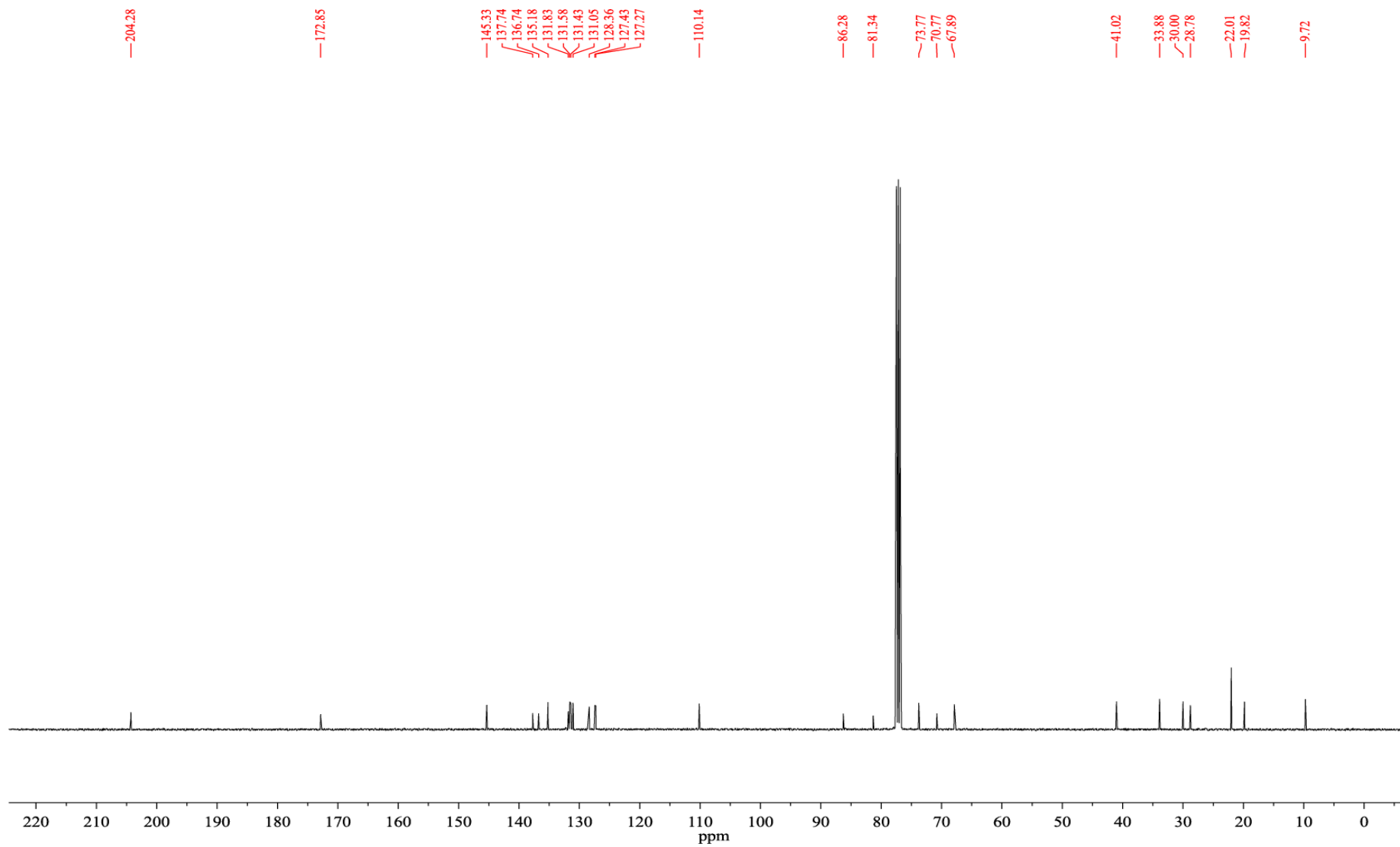
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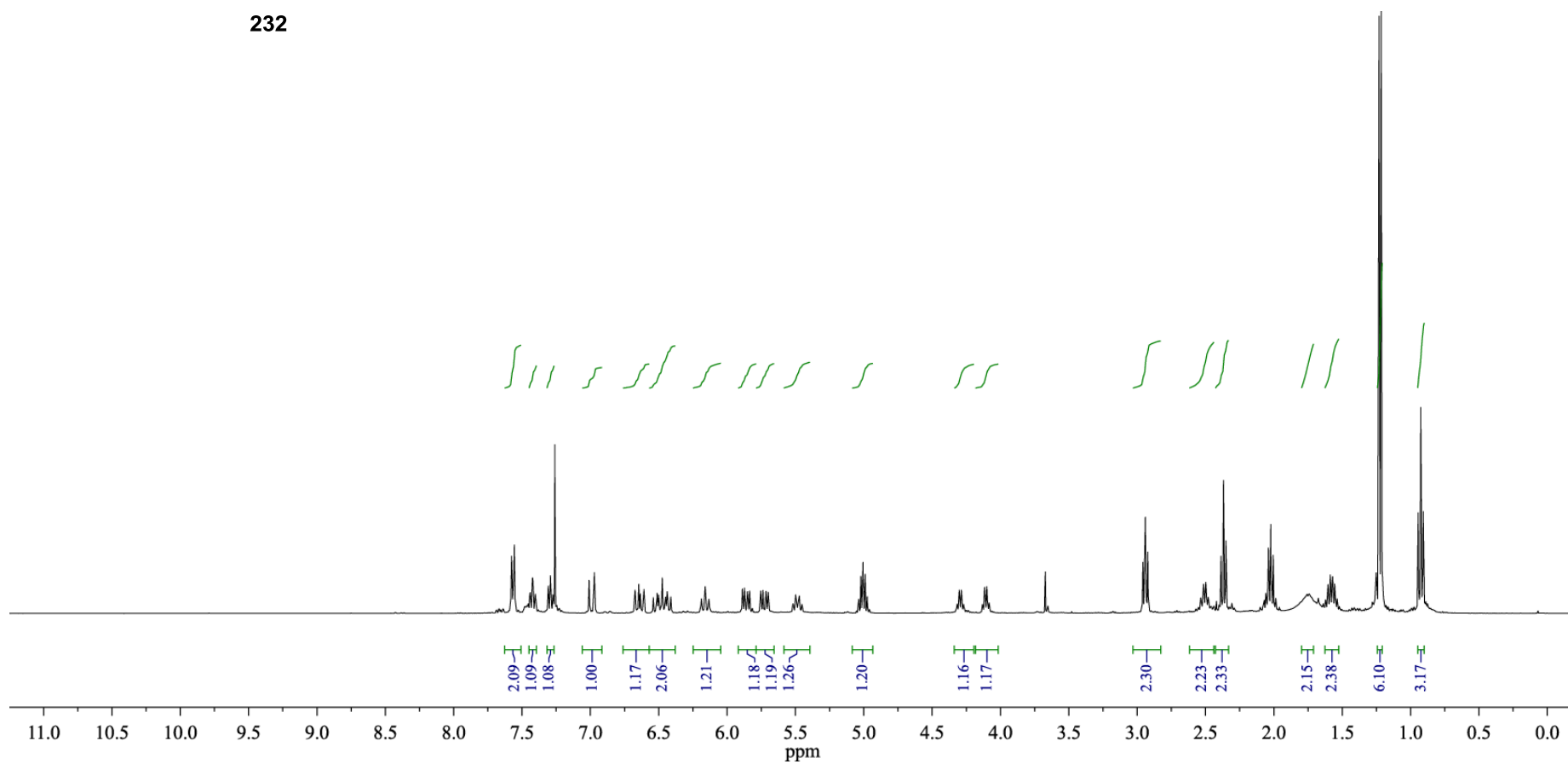


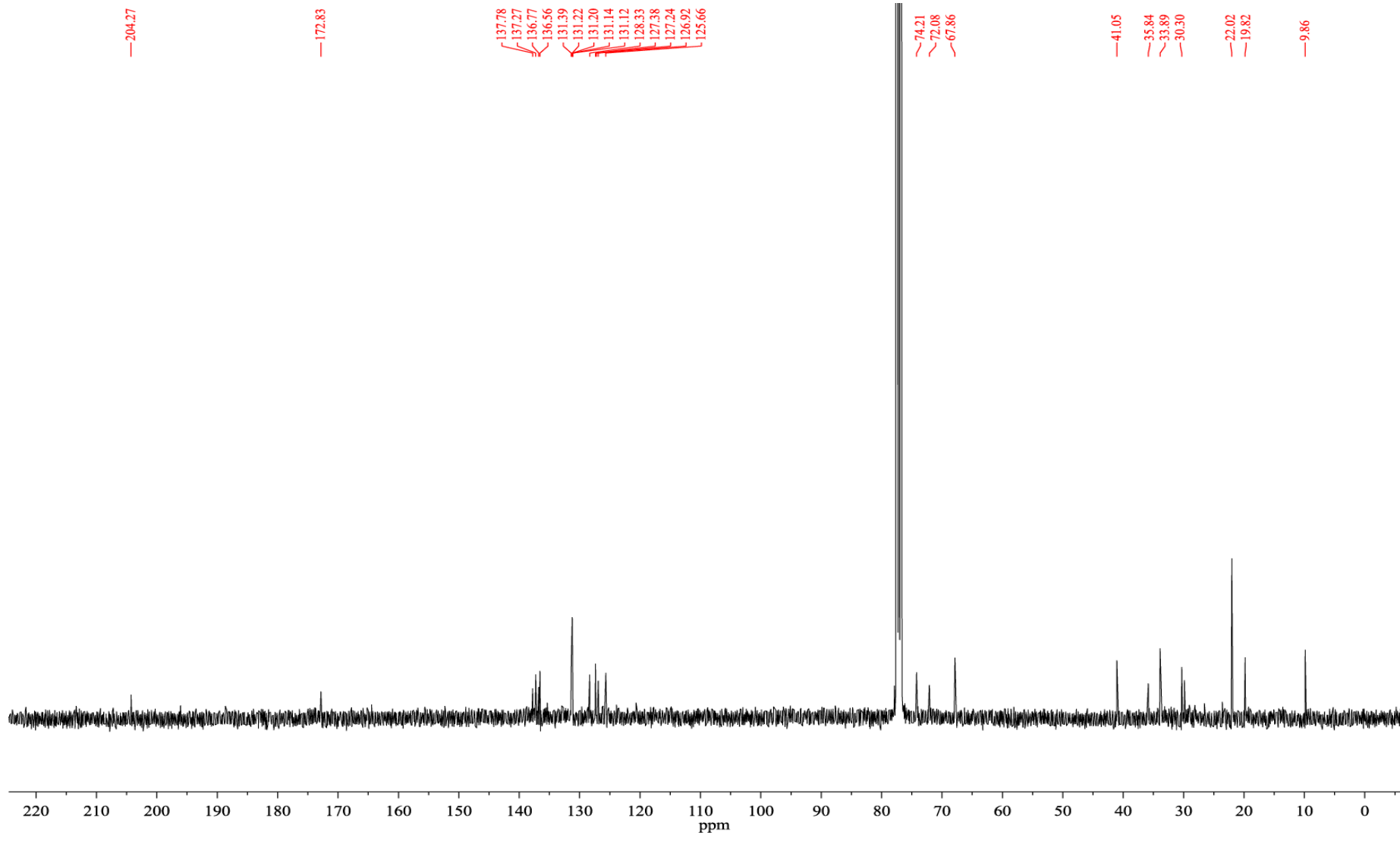


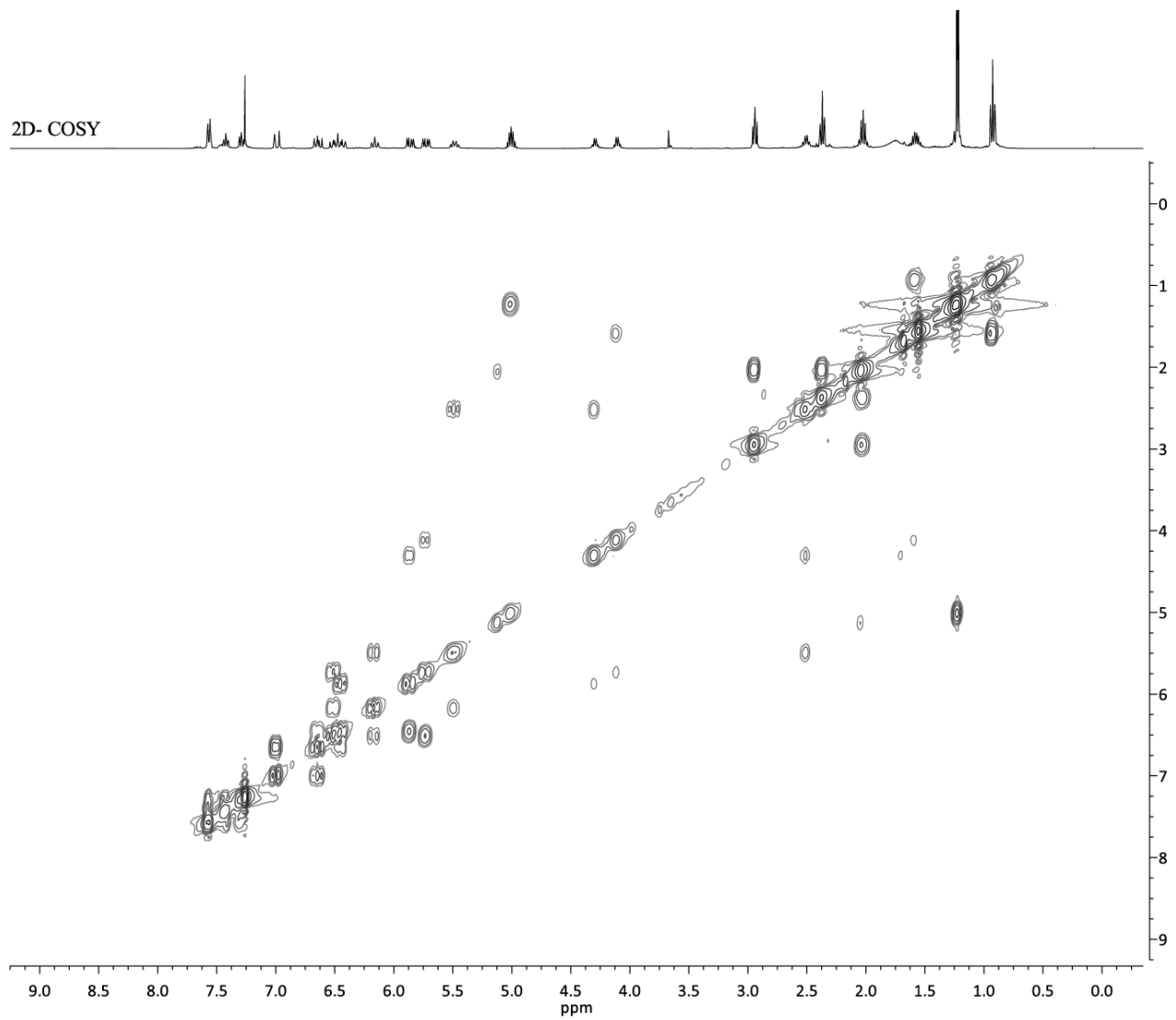


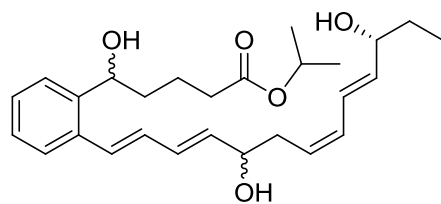




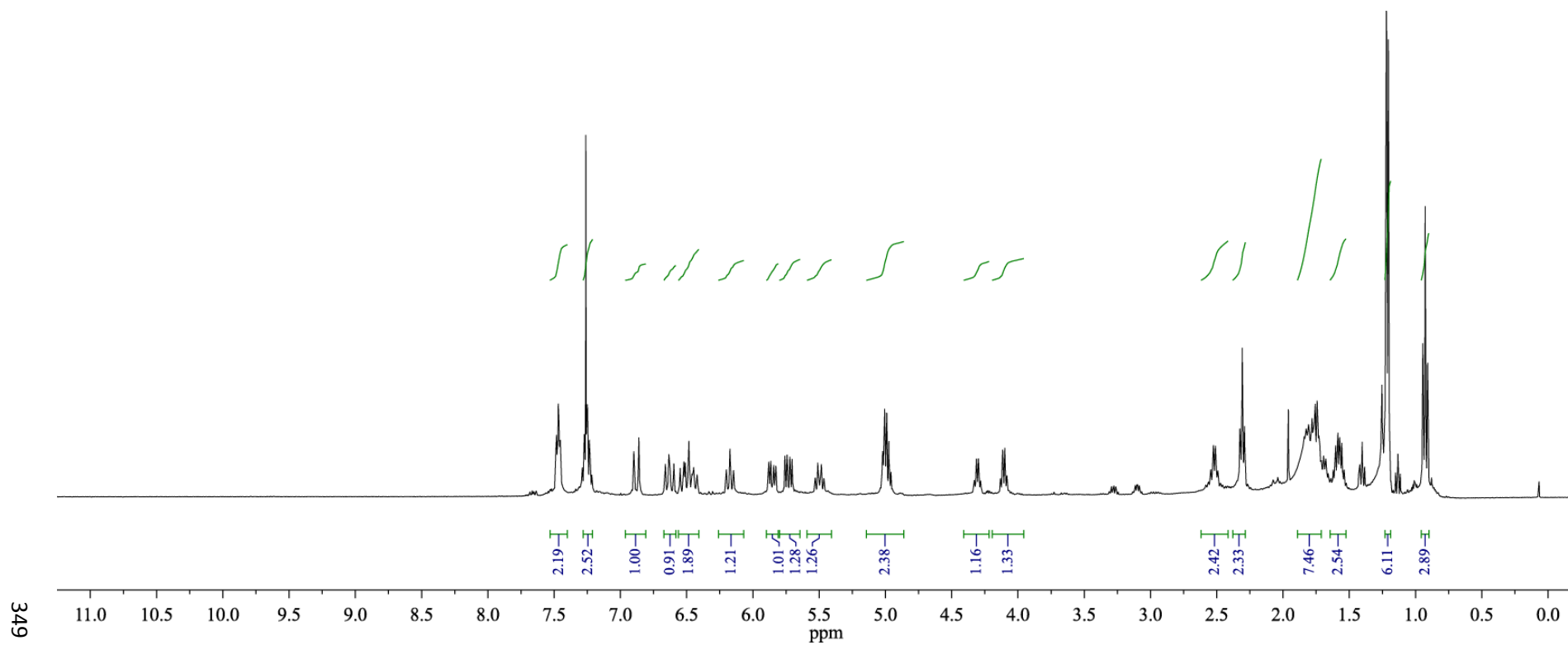




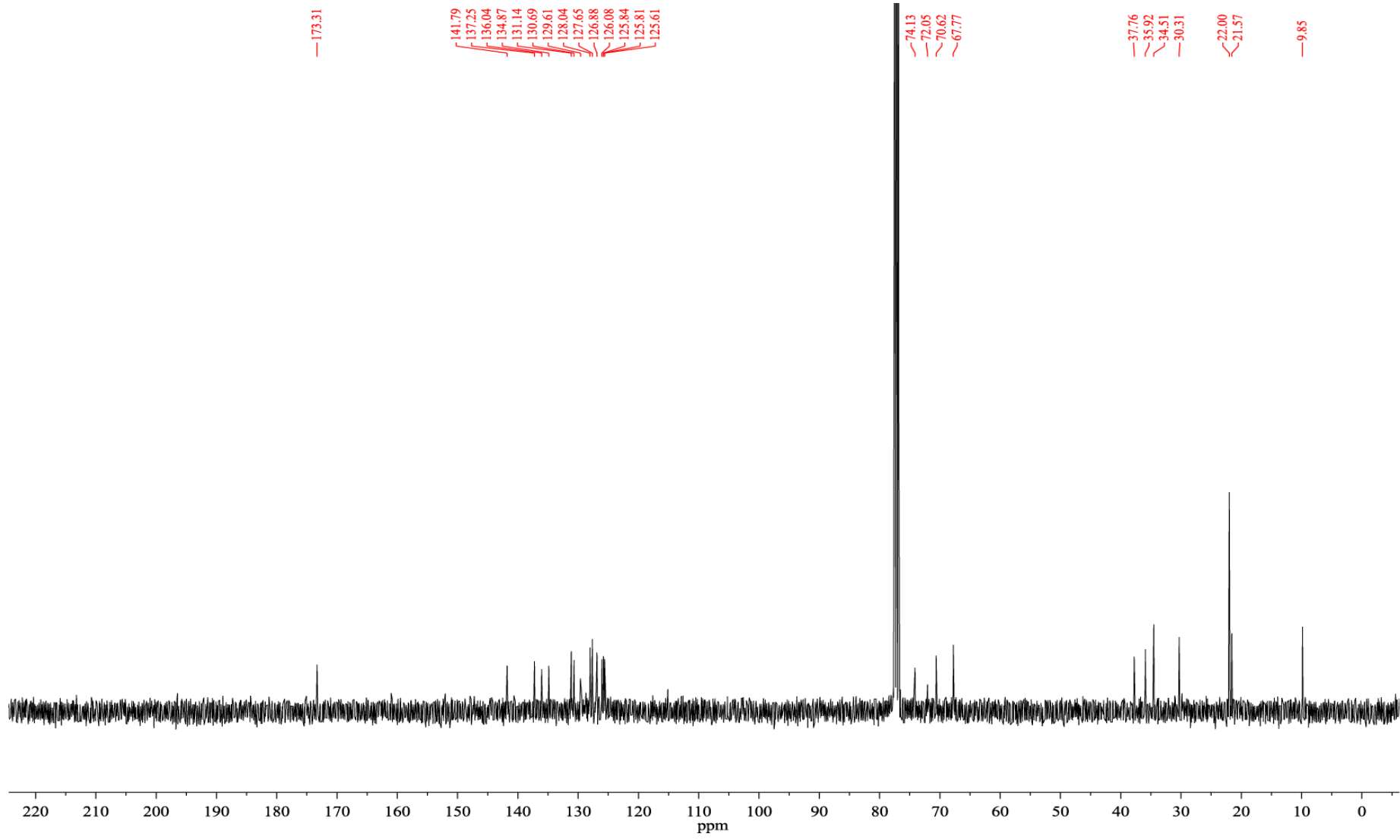


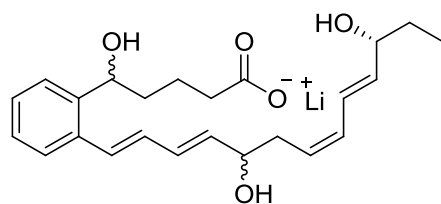


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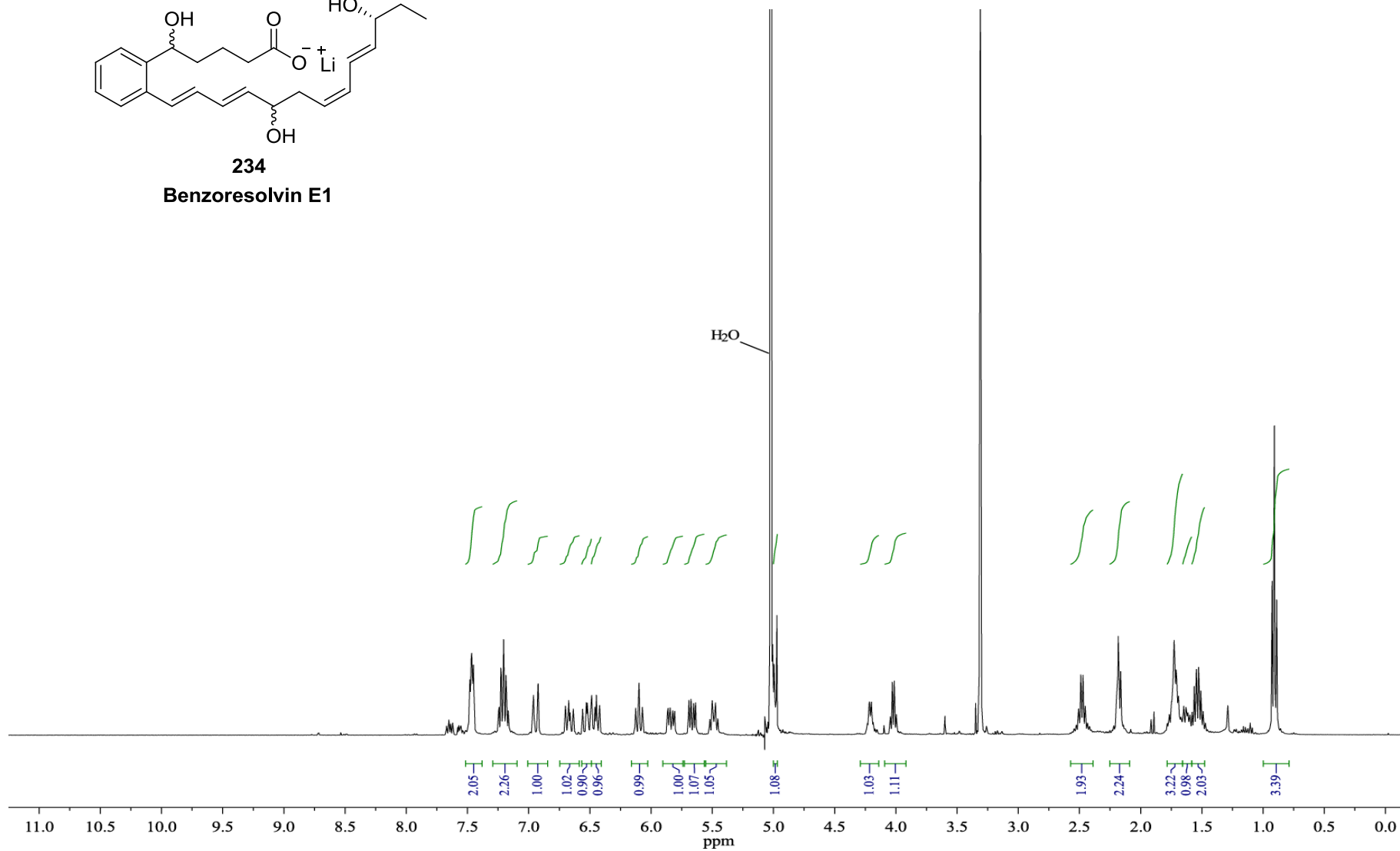
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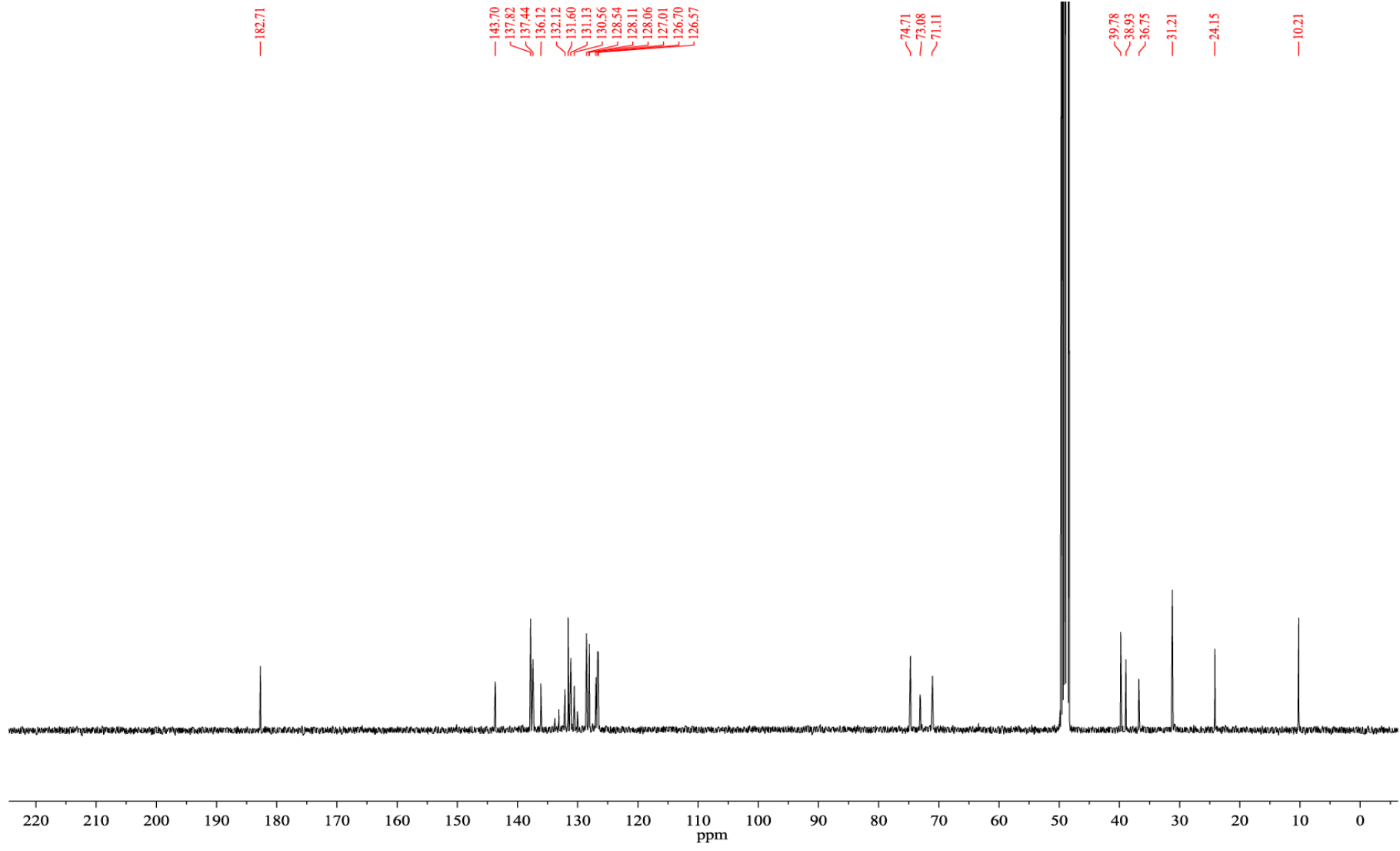


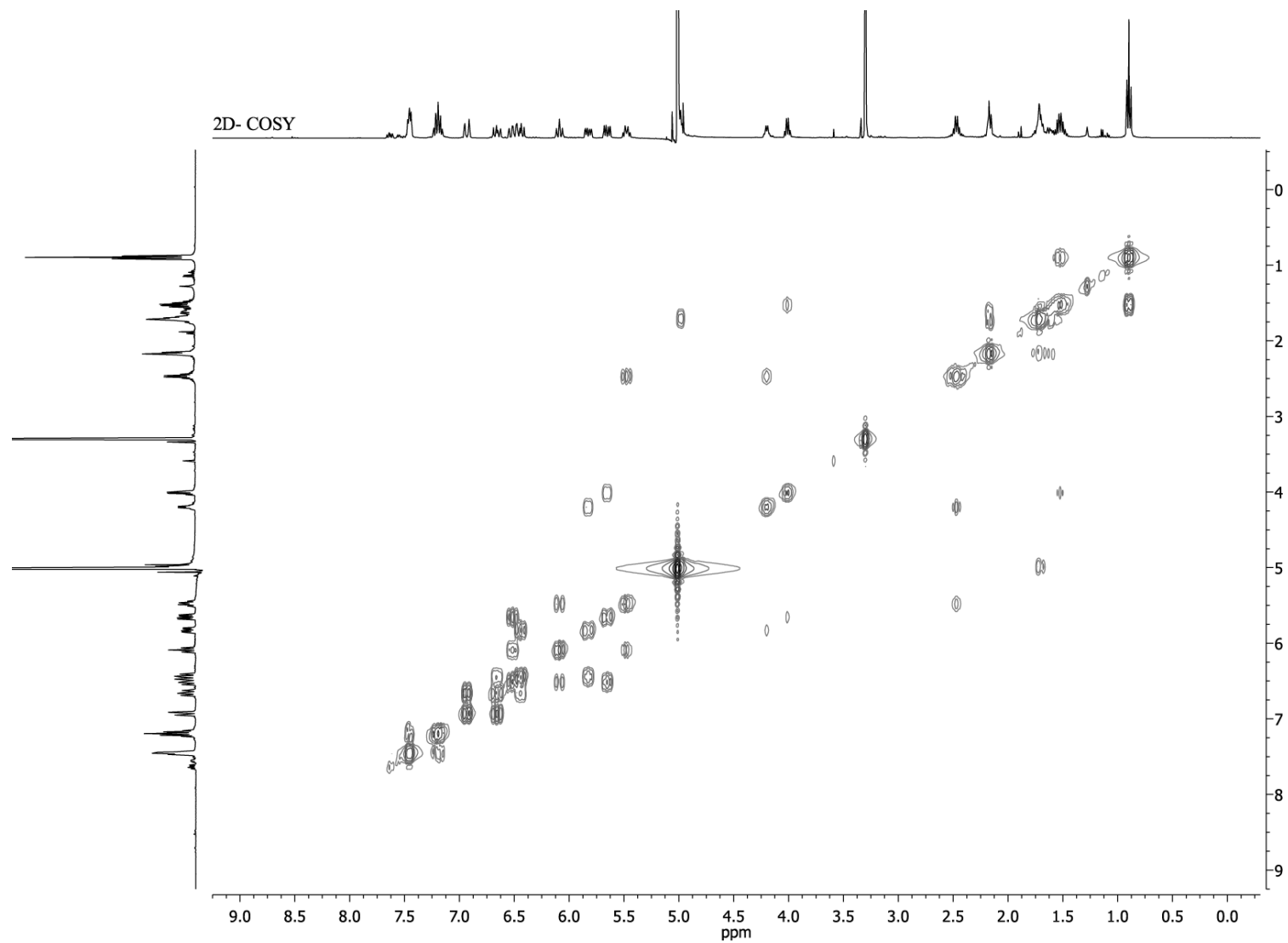


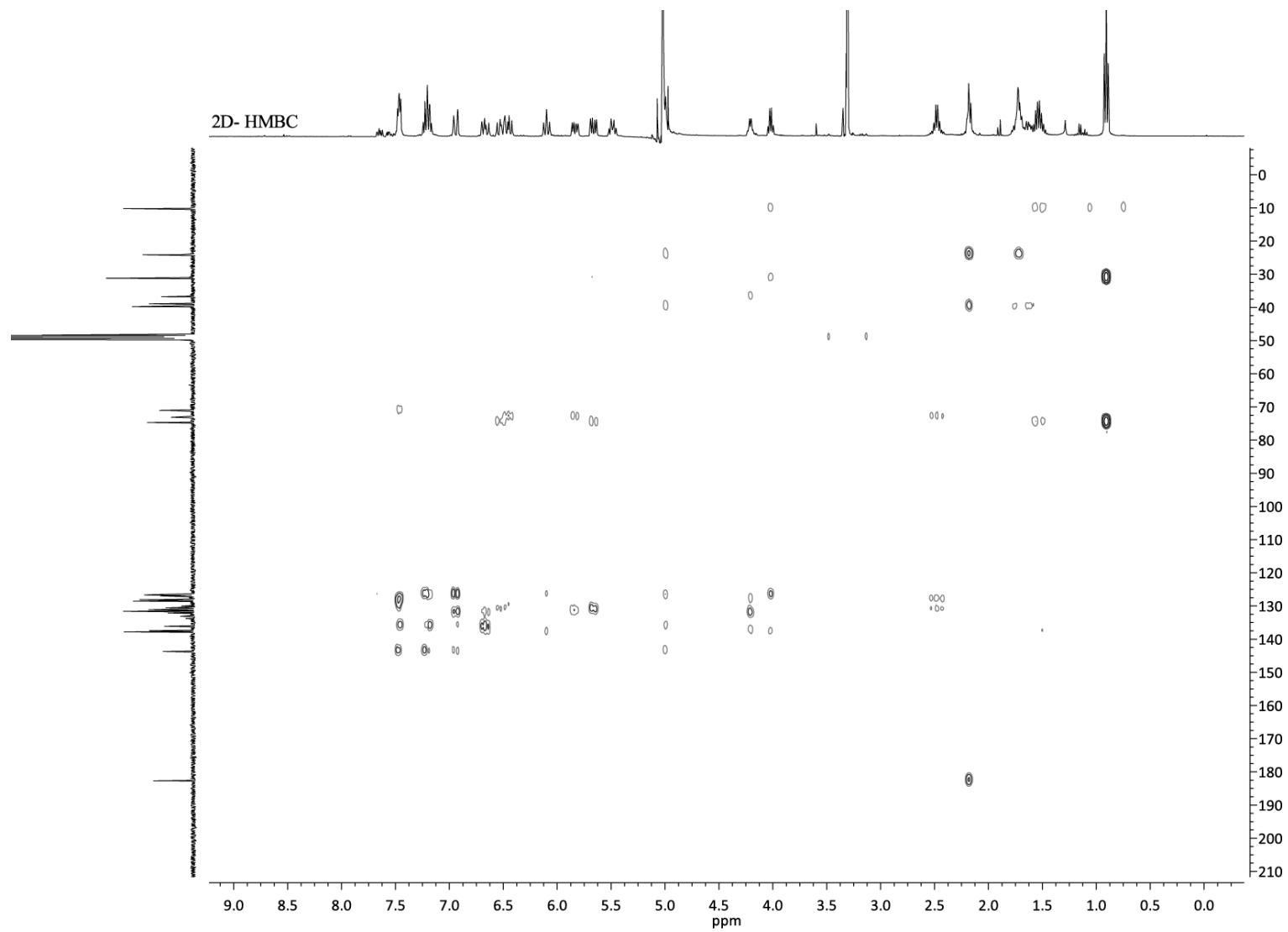
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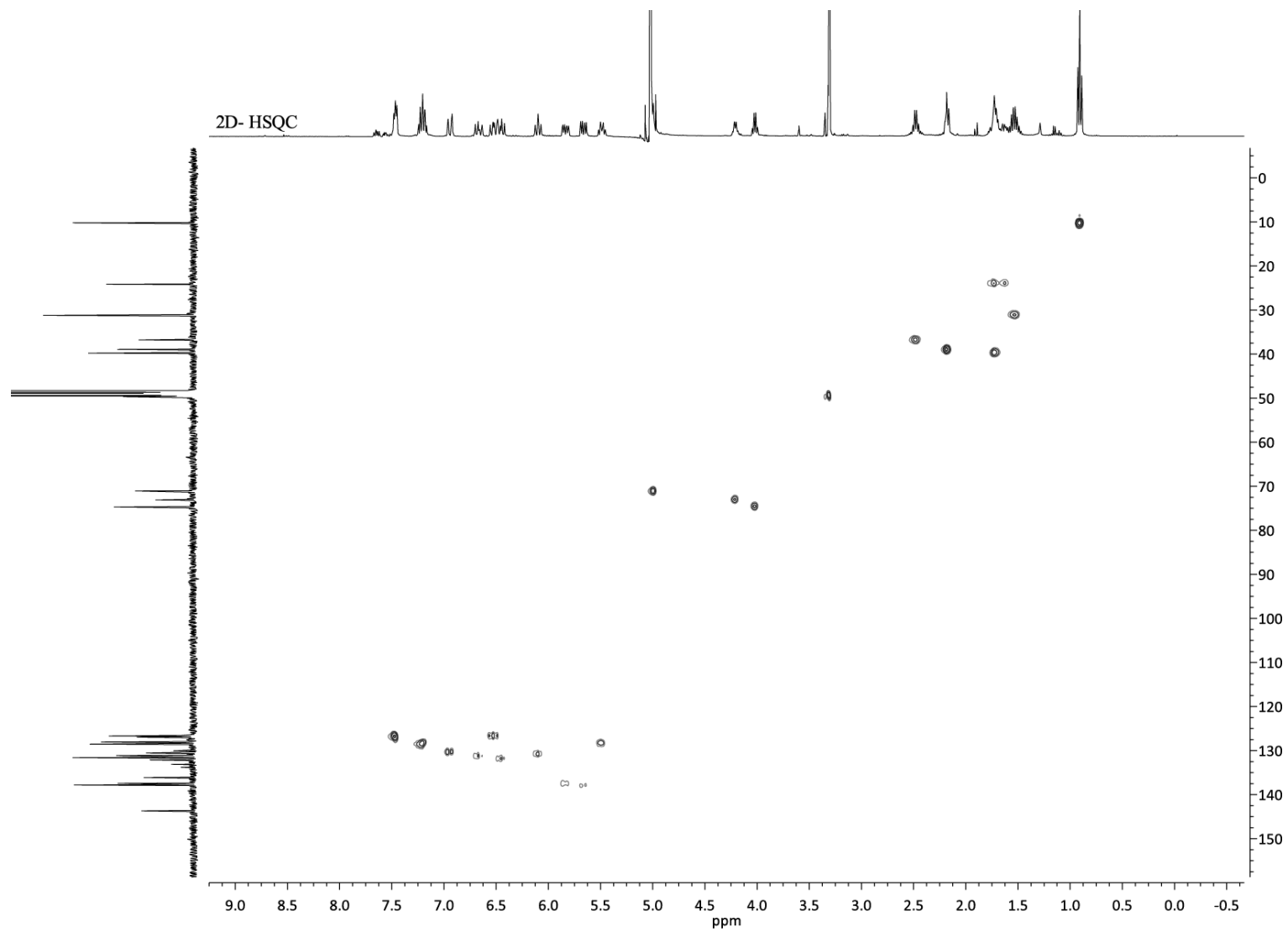
Benzoeresolvin E1







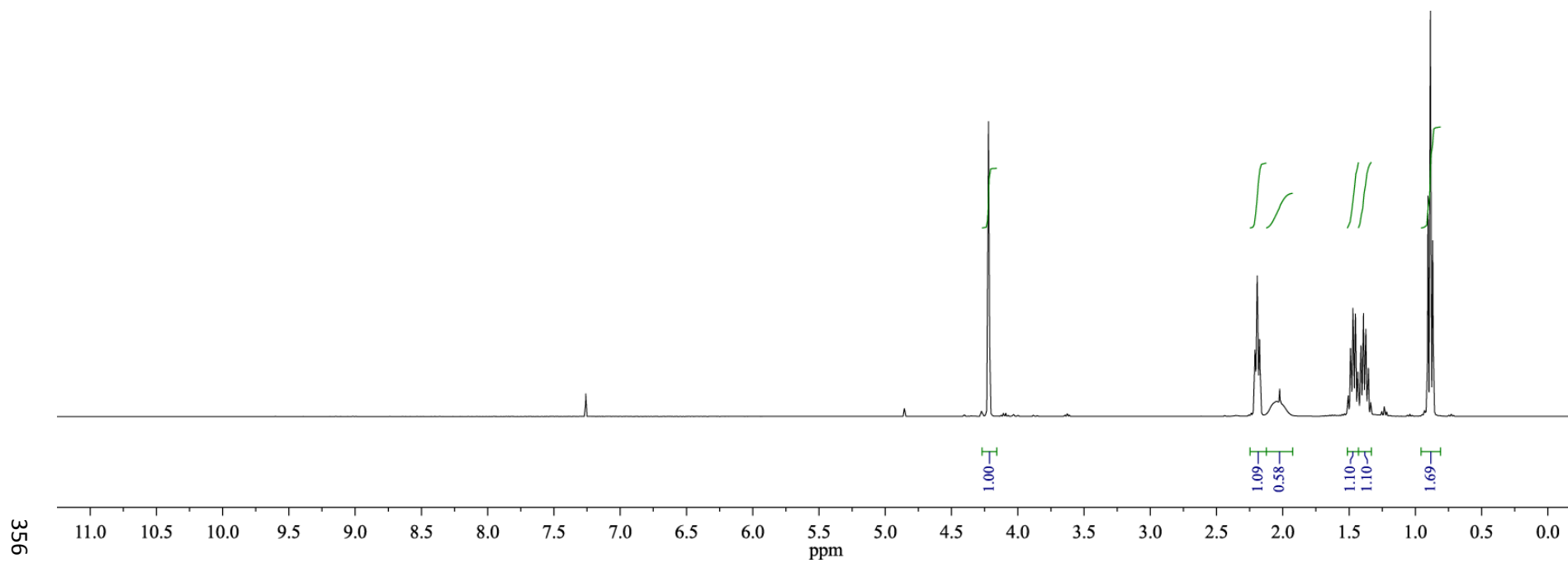


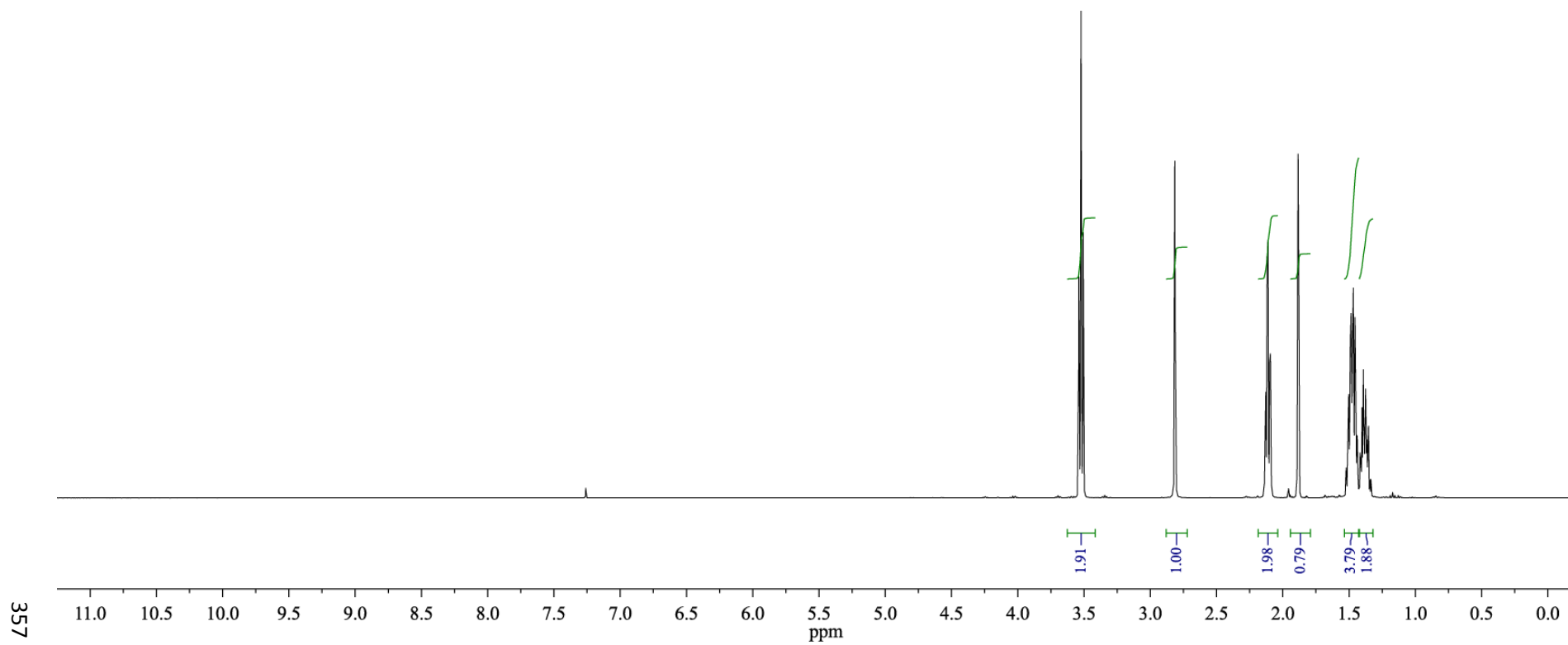
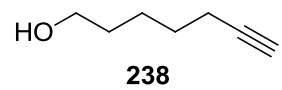


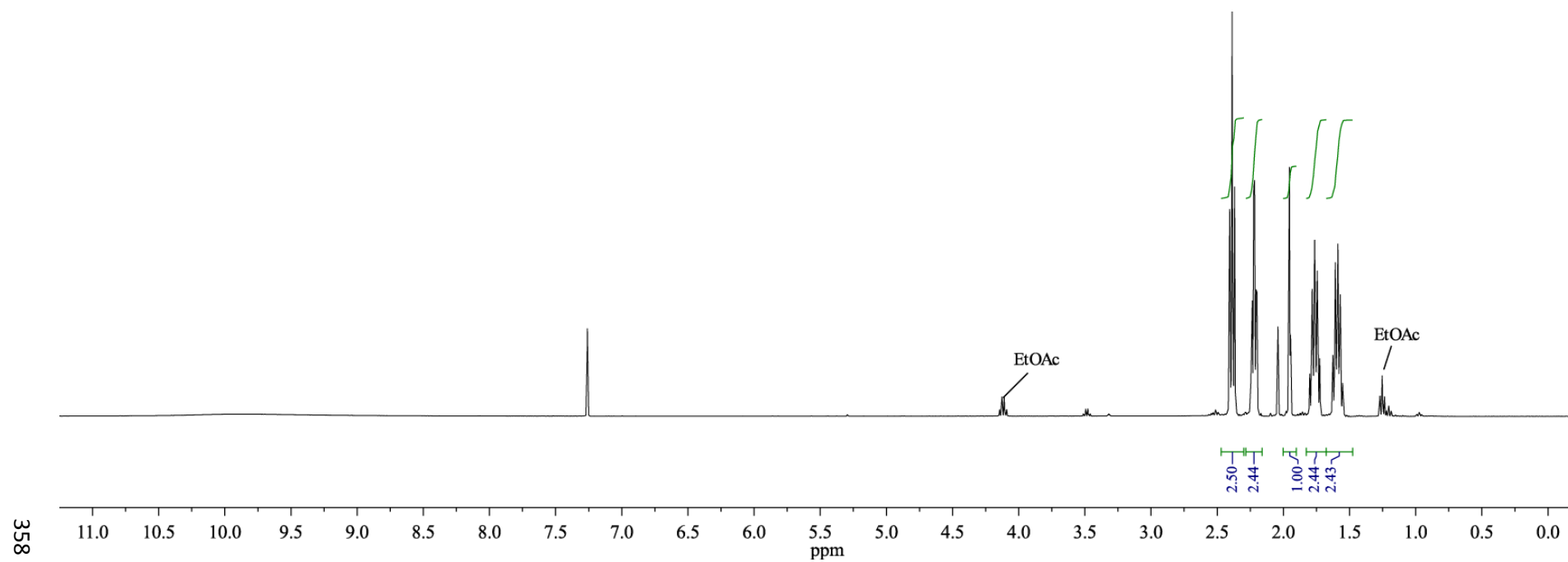
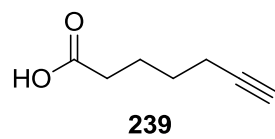
Chapter 5 spectra

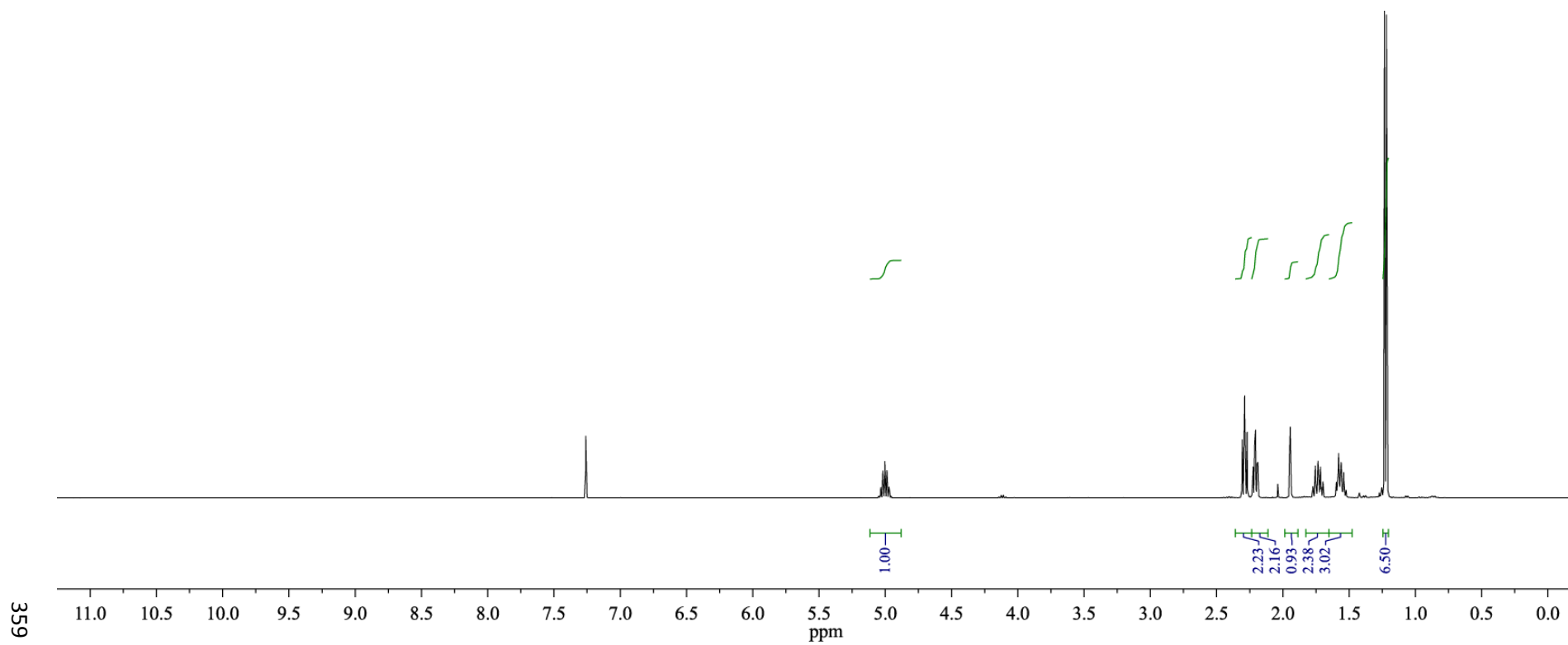
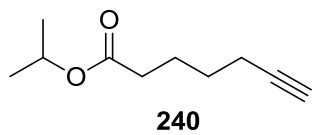


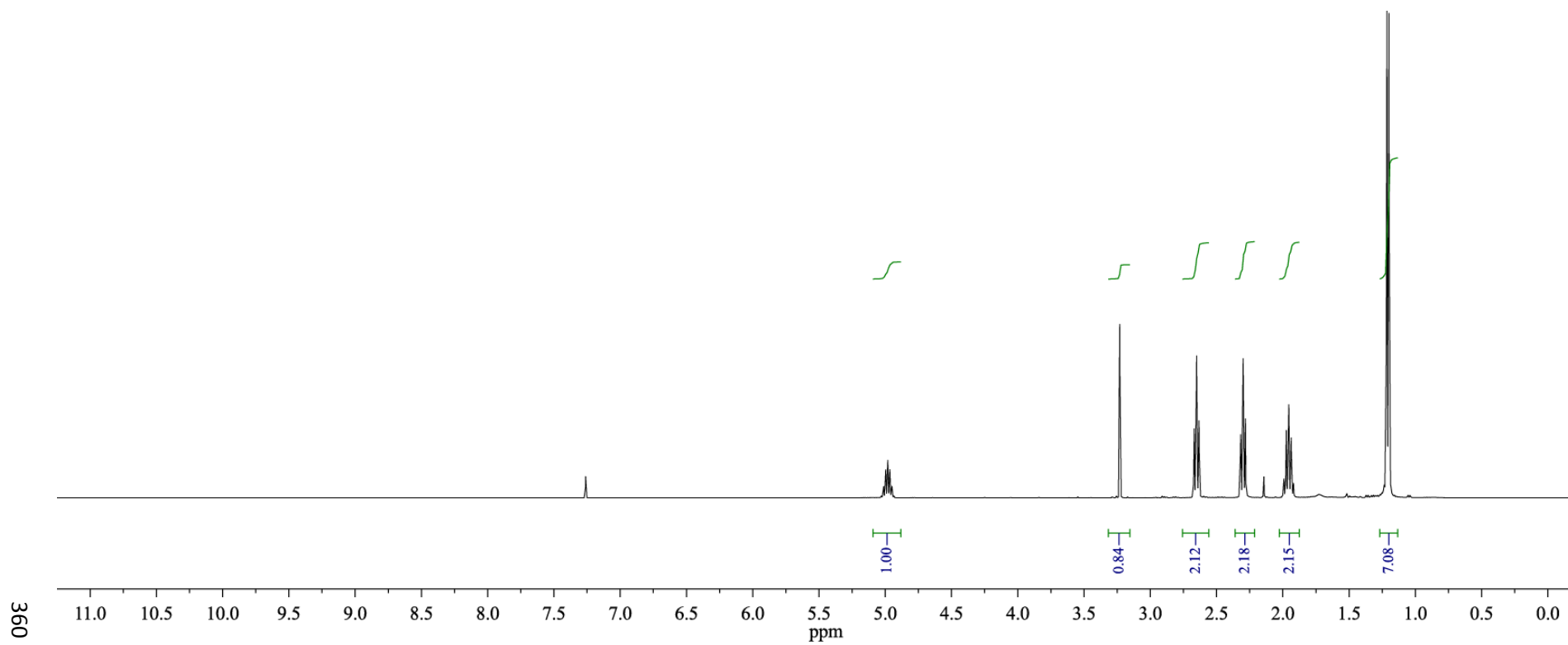
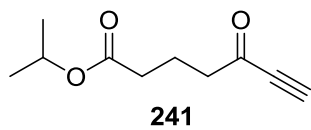
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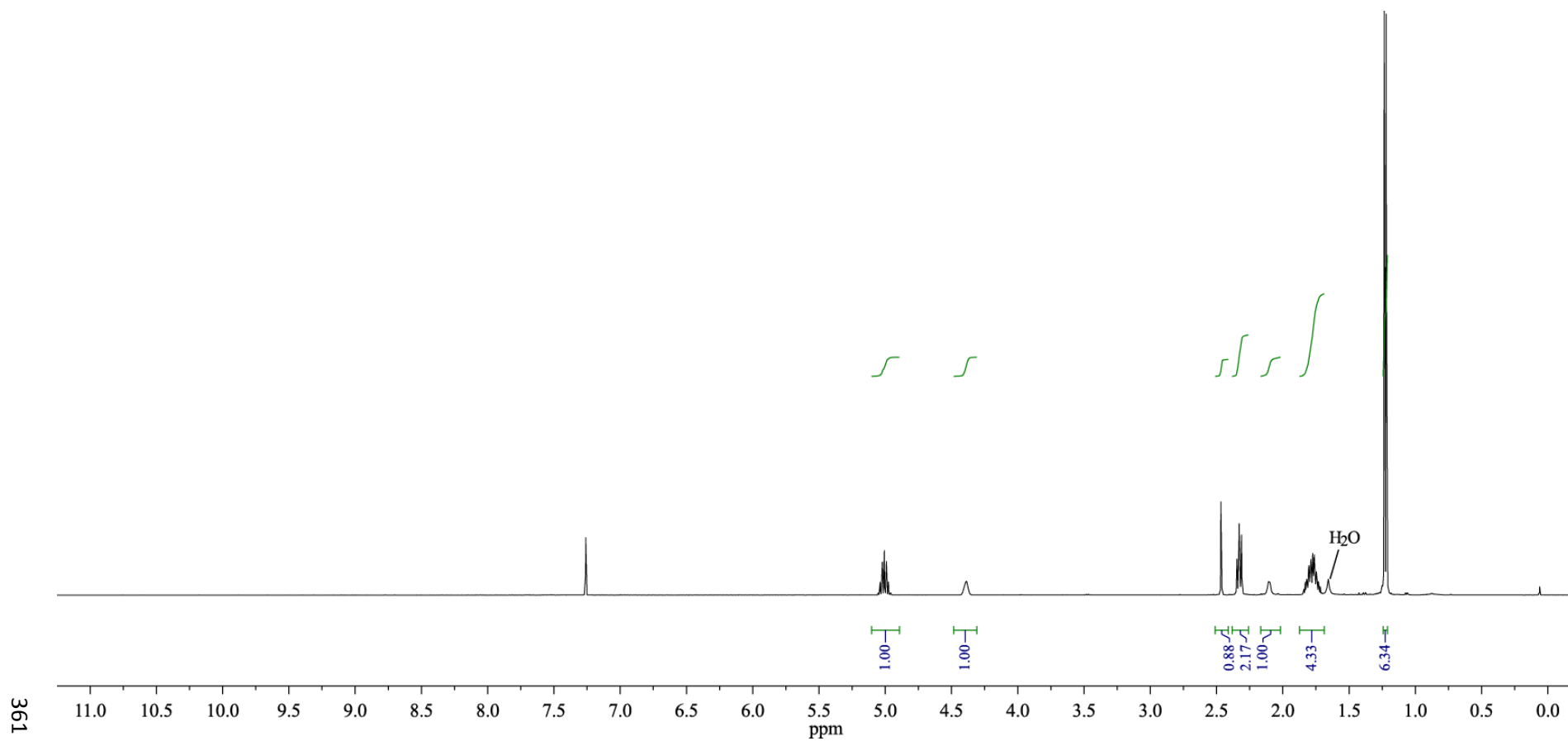
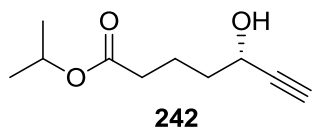


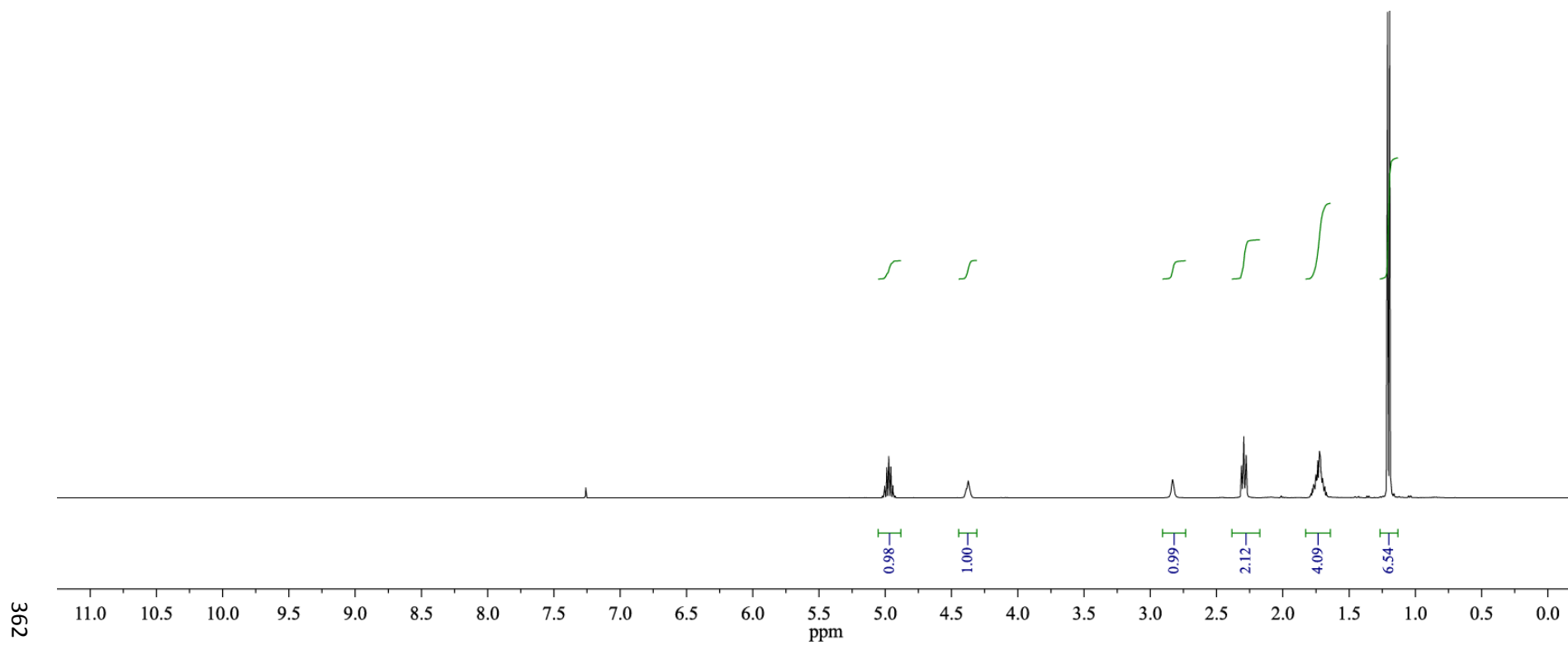
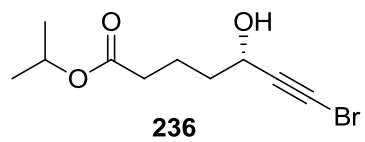


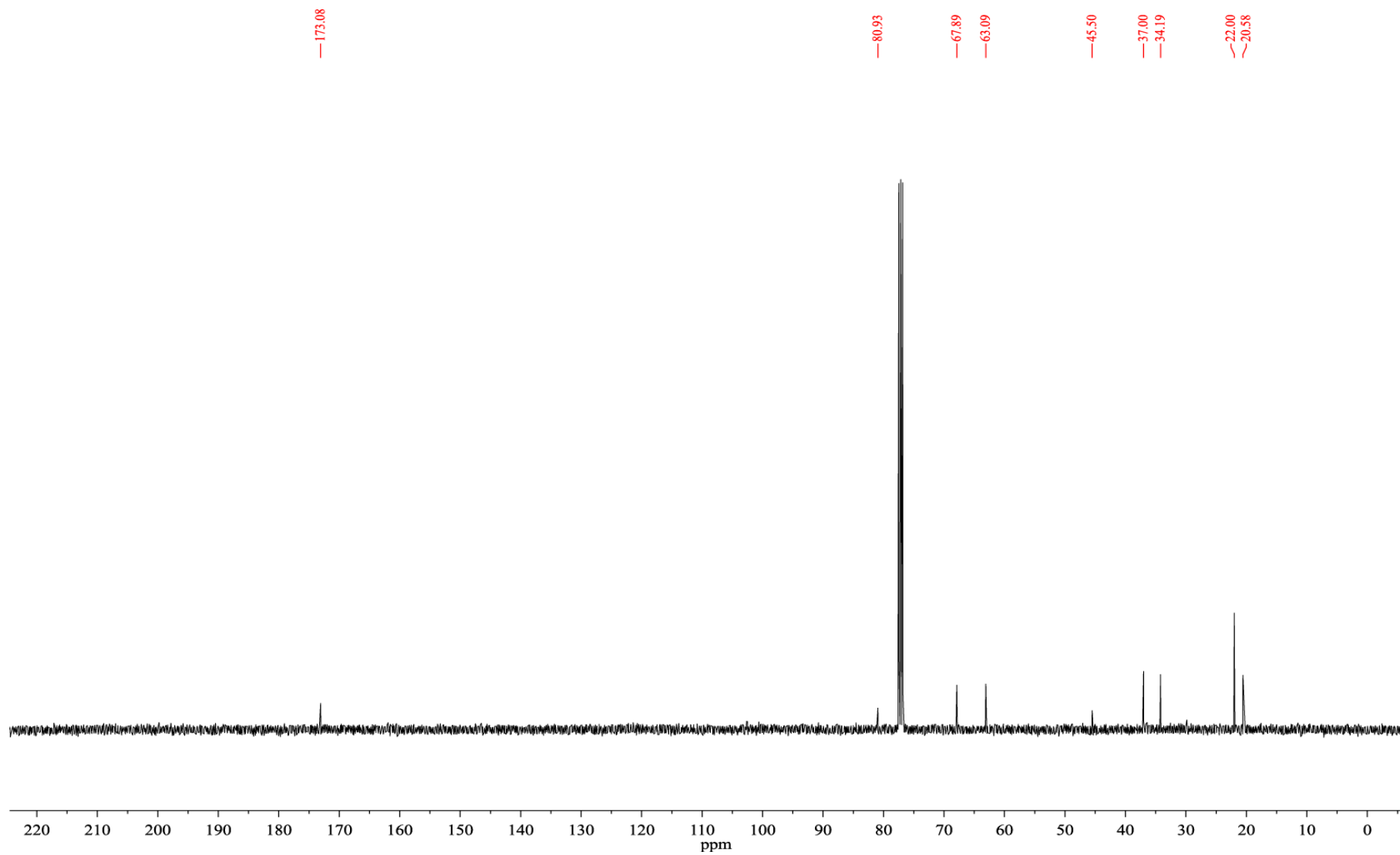


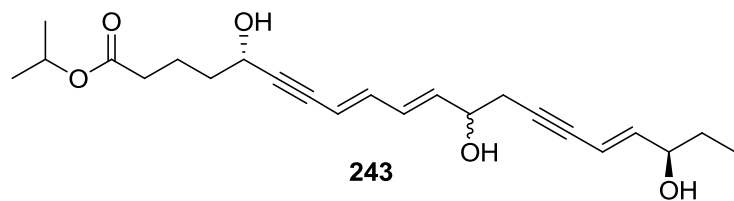








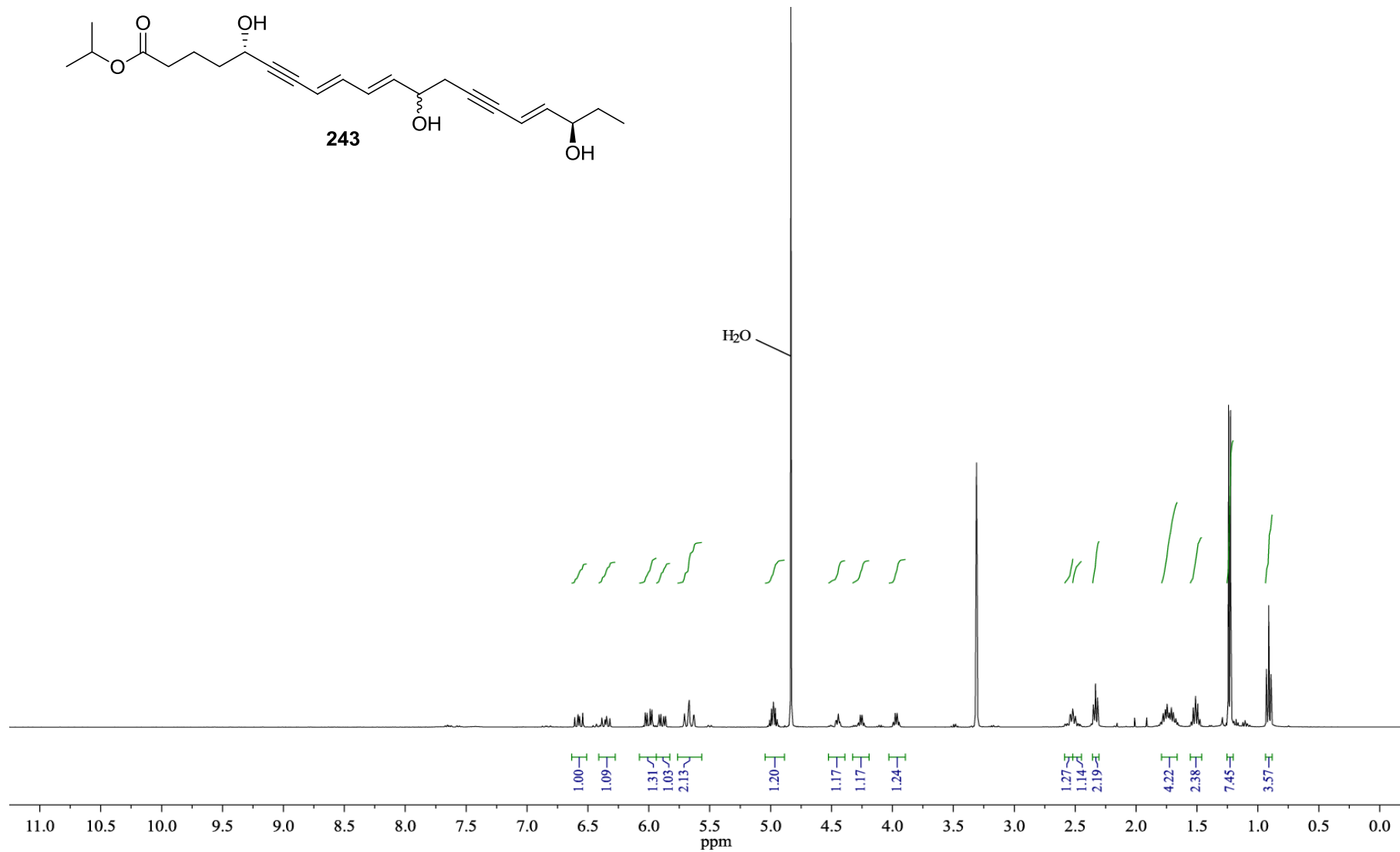




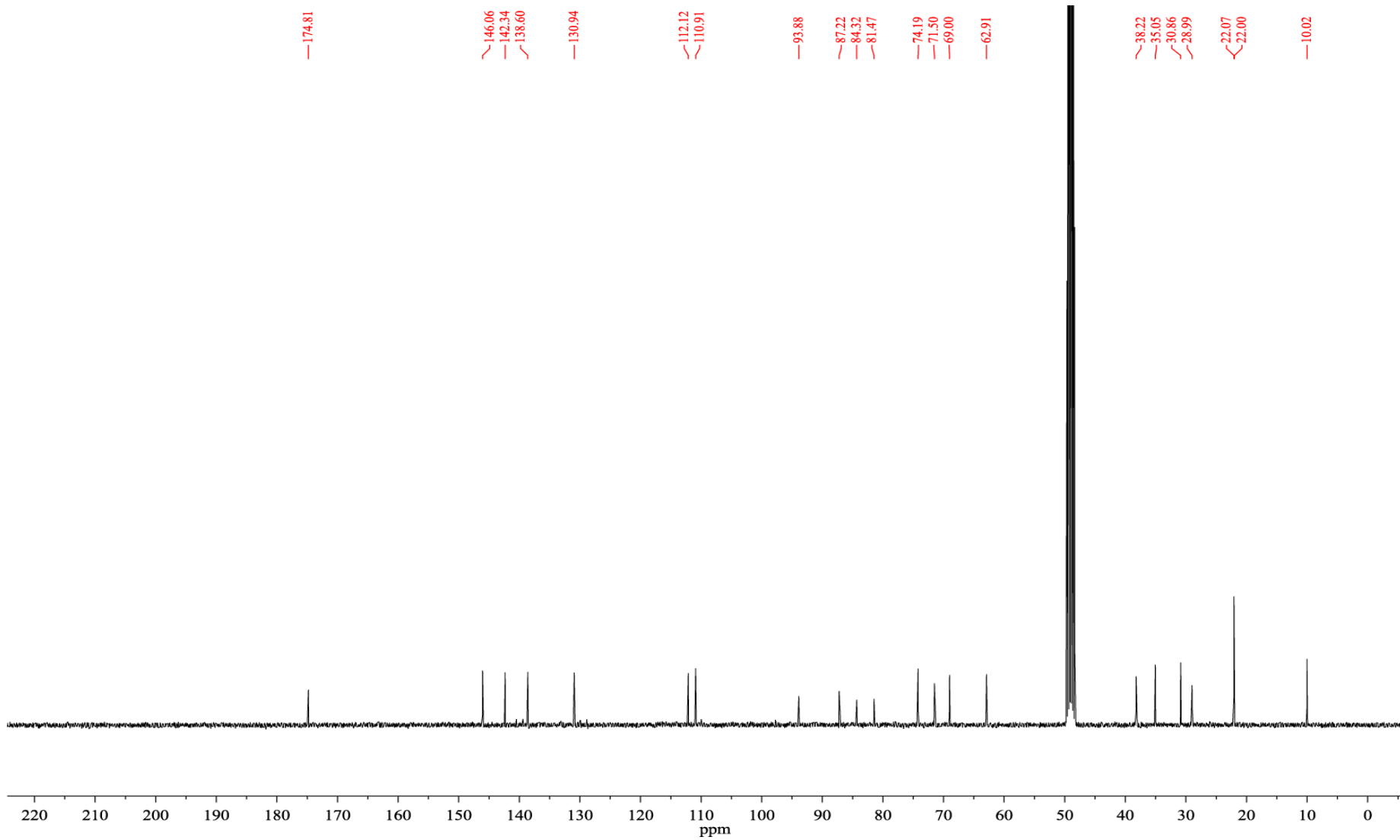
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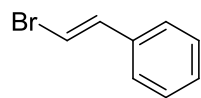
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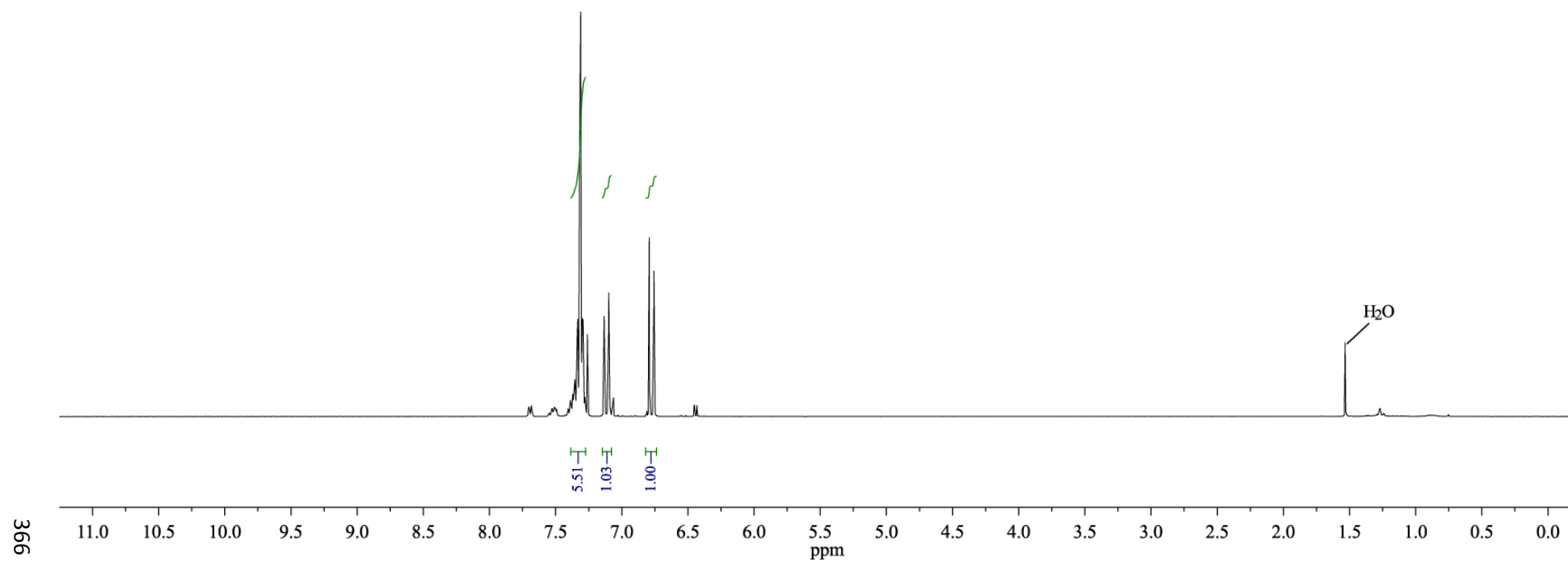
596

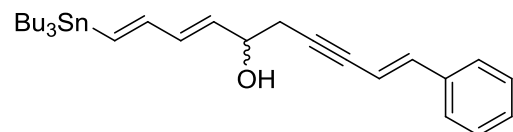


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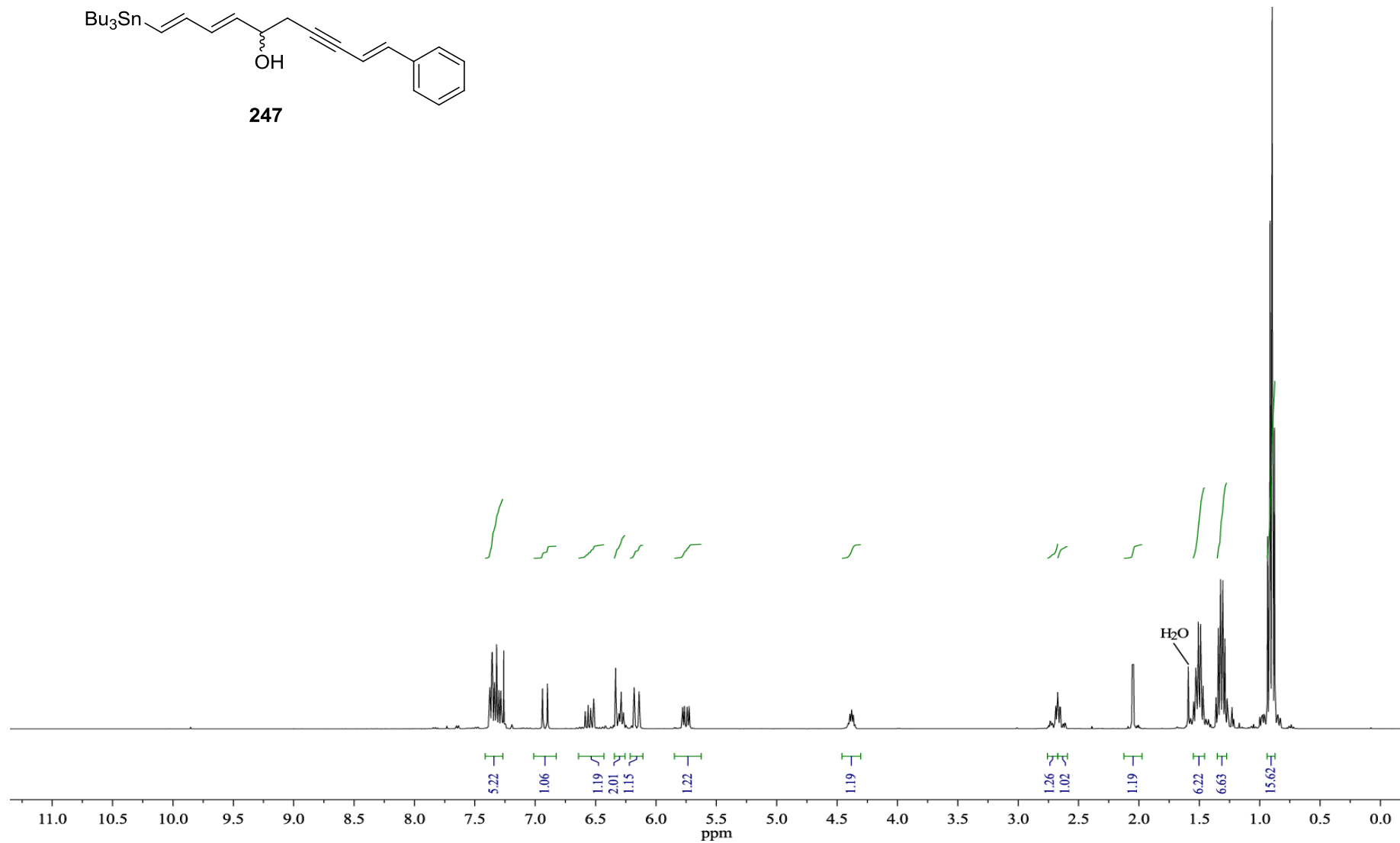


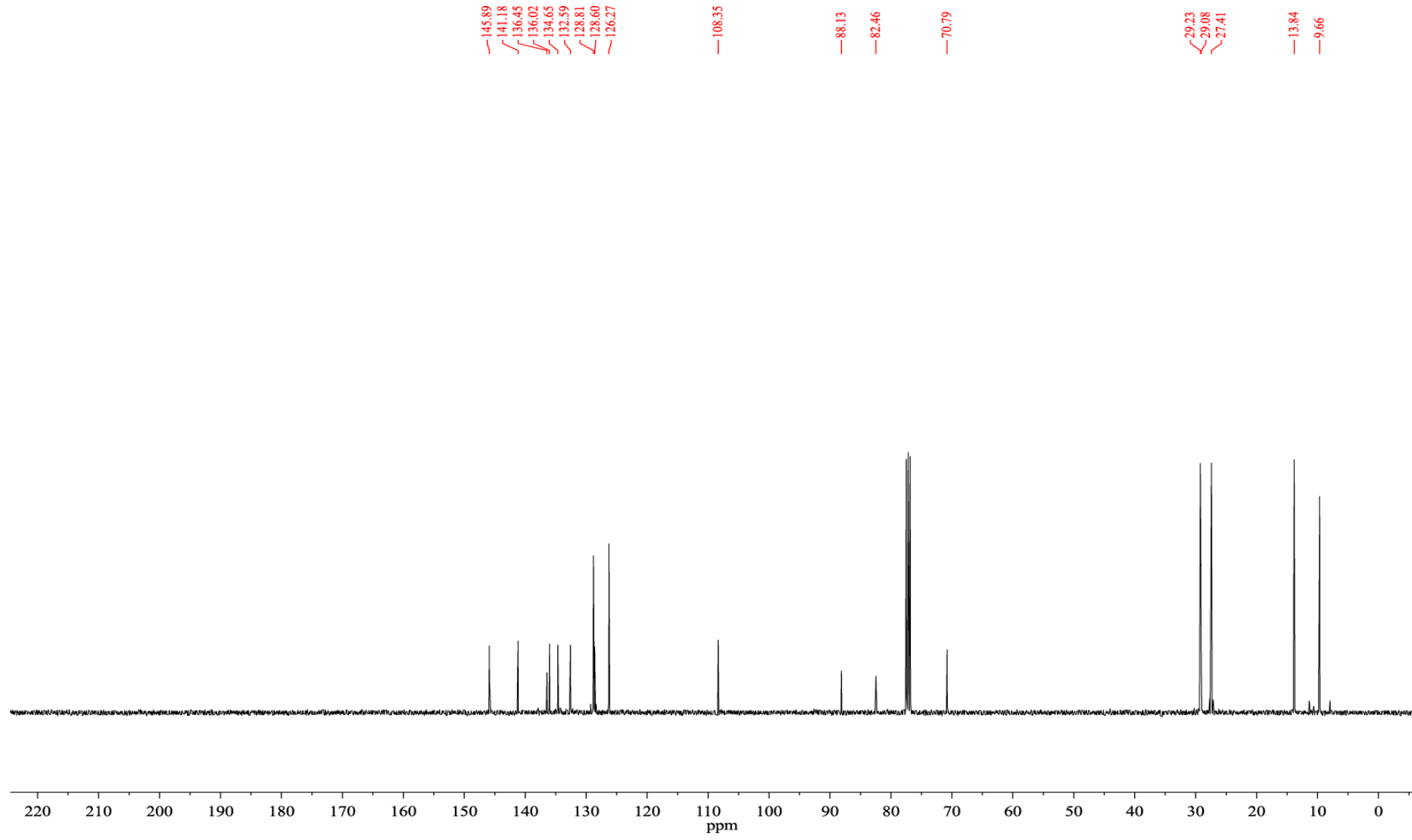
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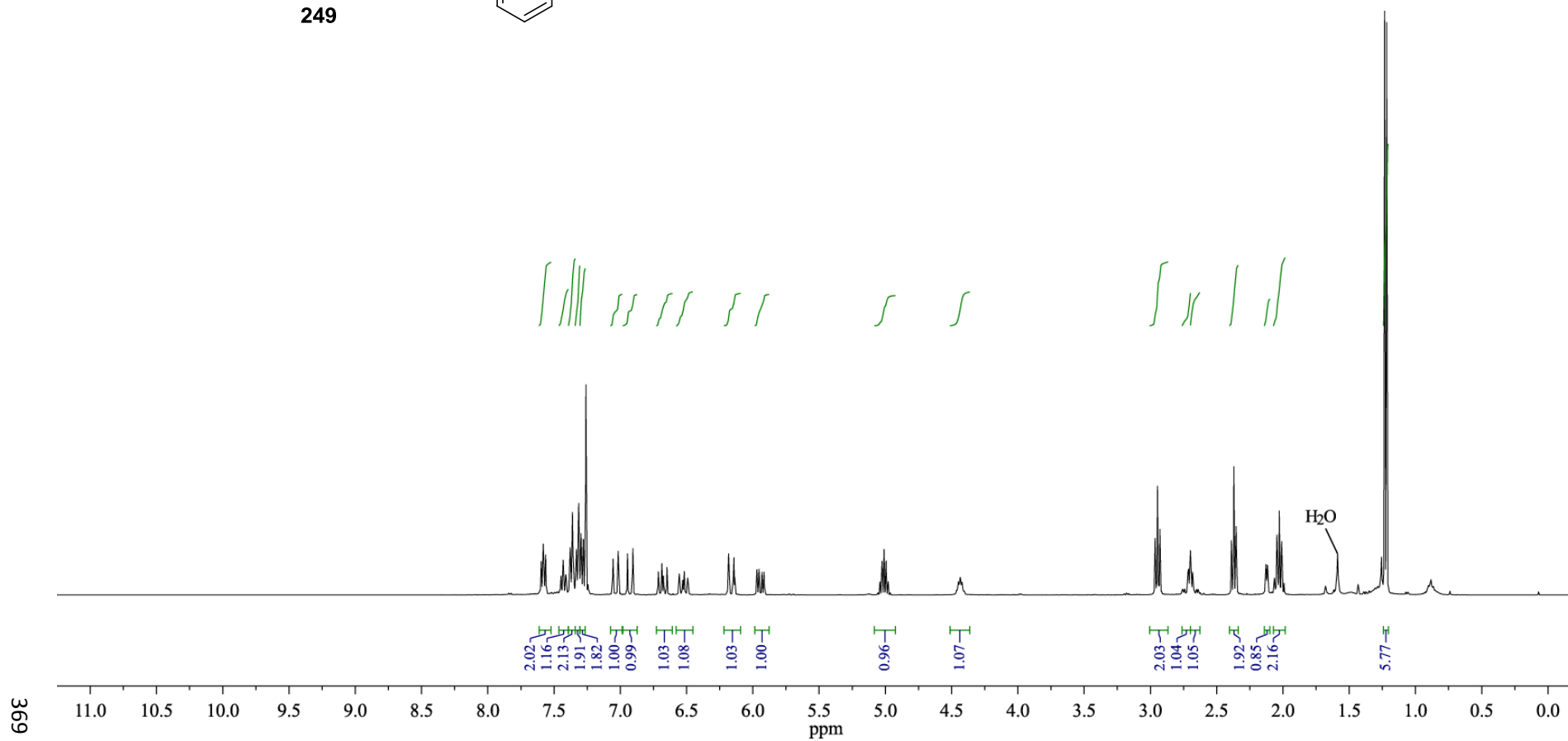
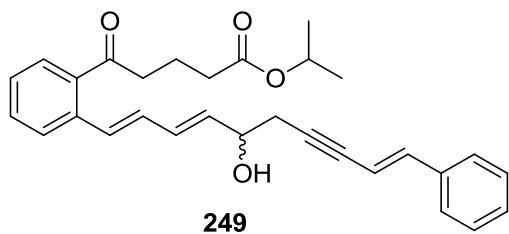


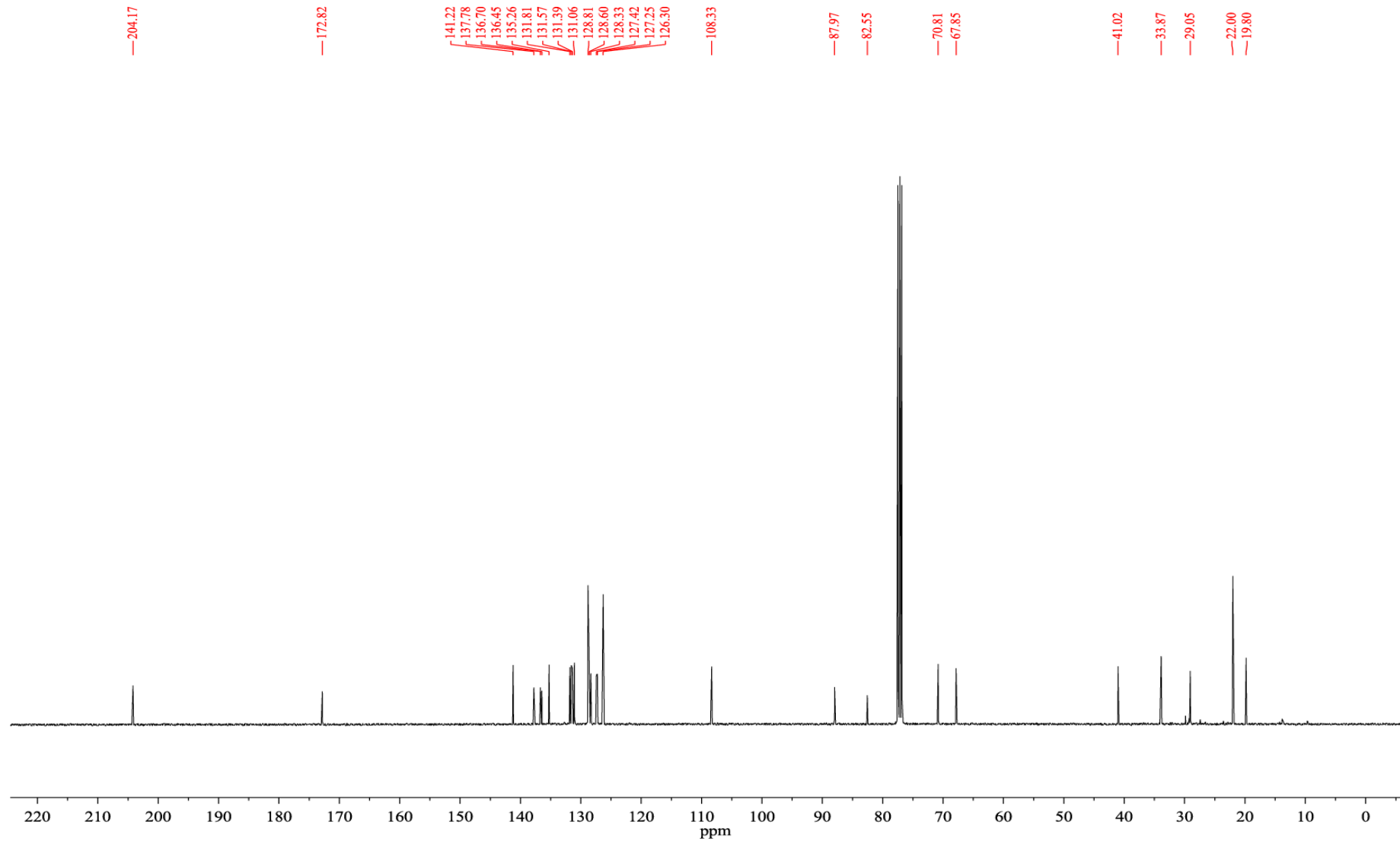


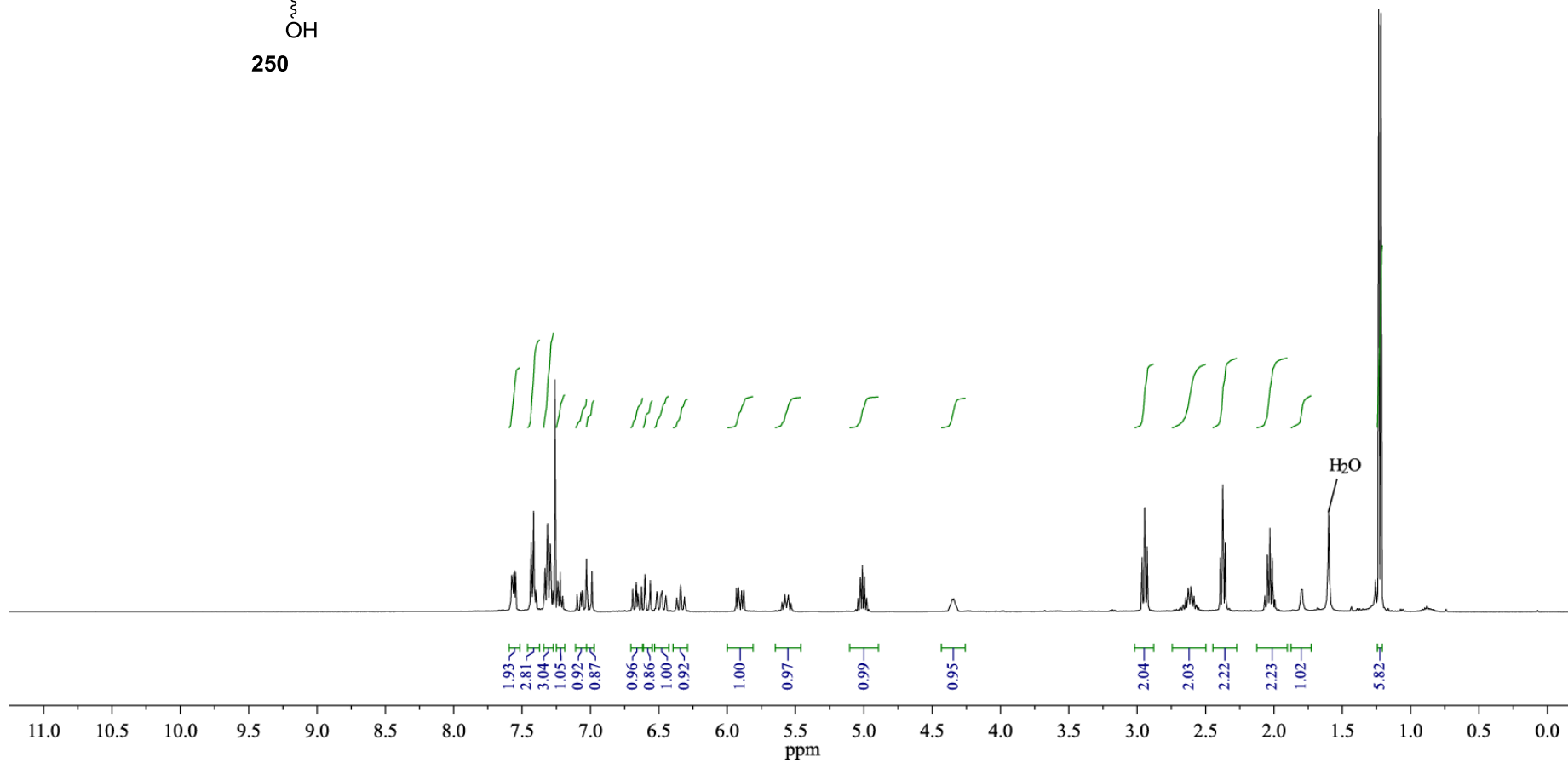
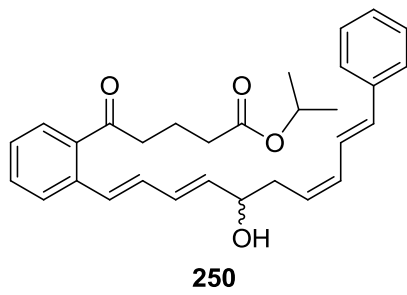
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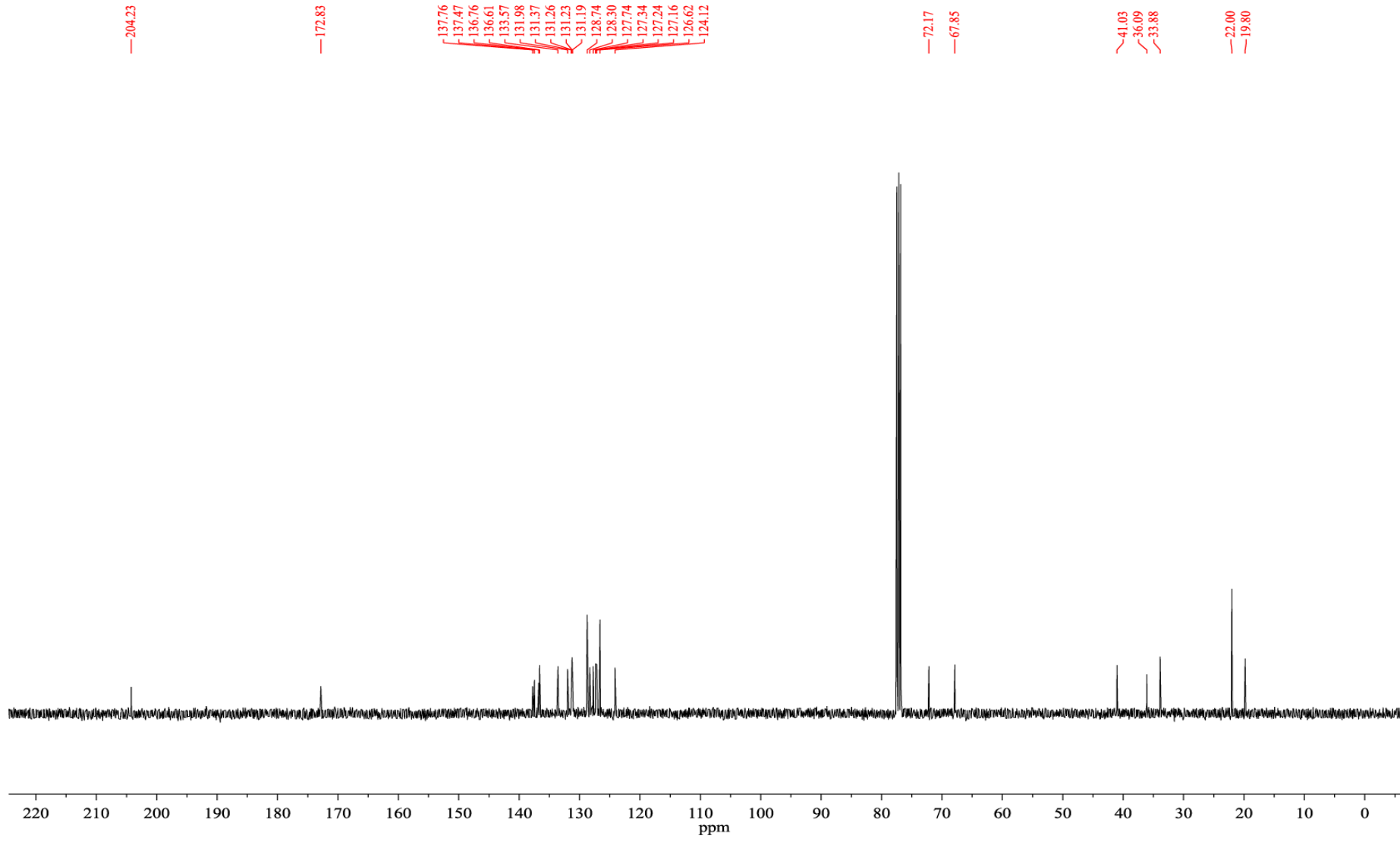


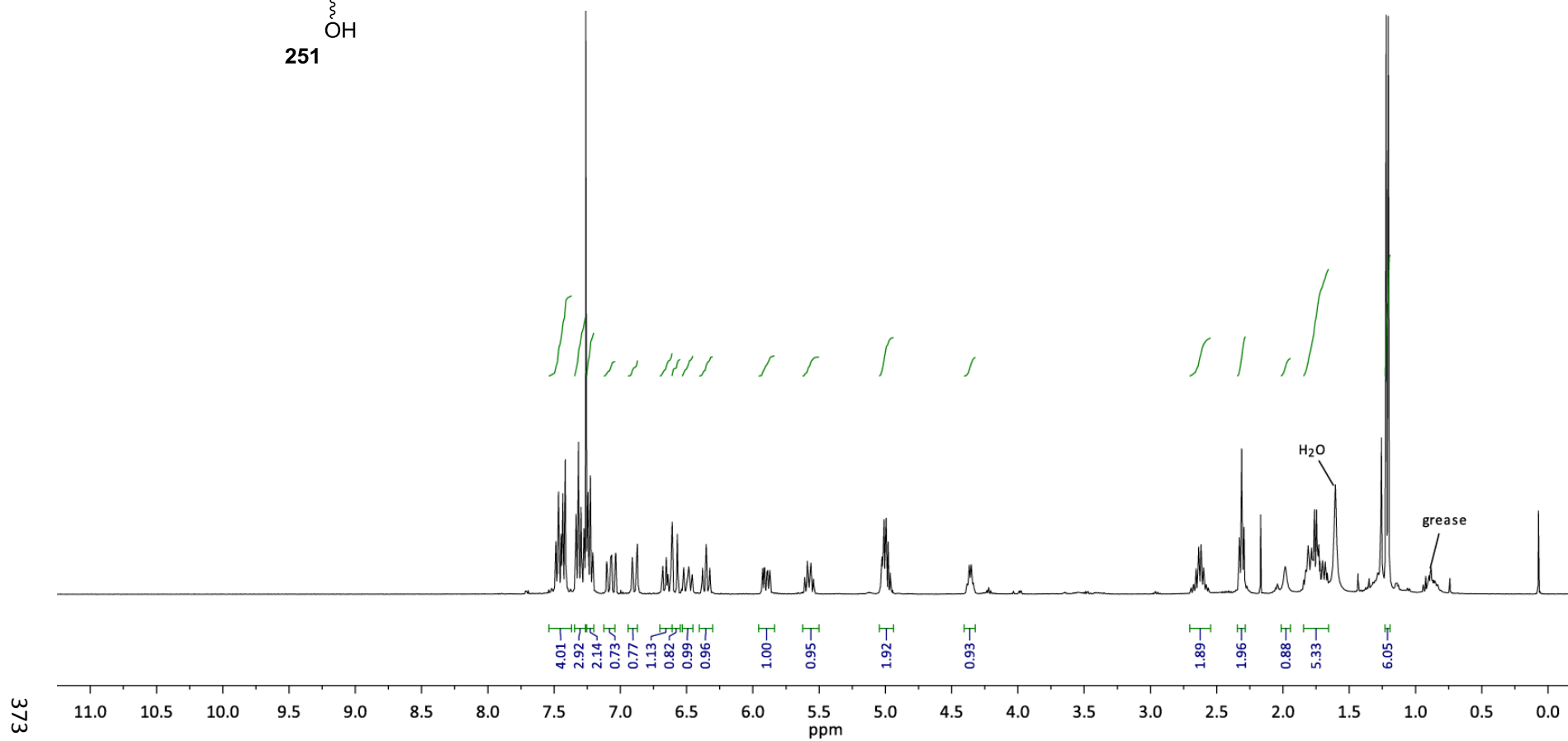
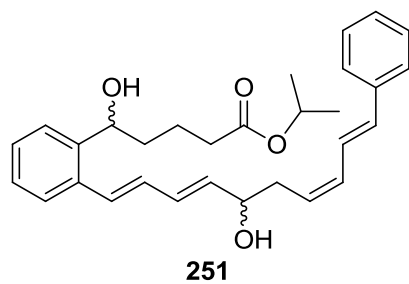


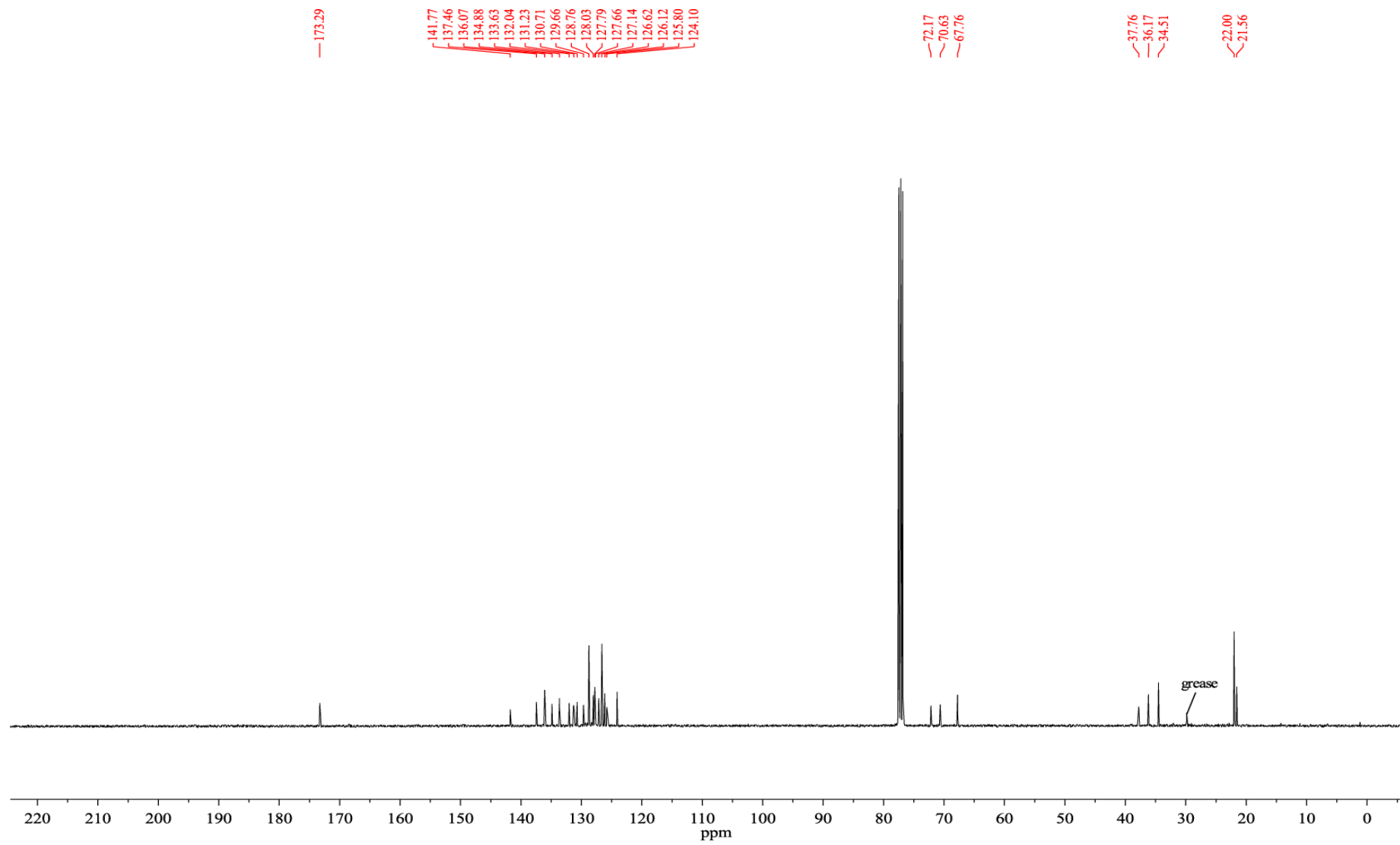




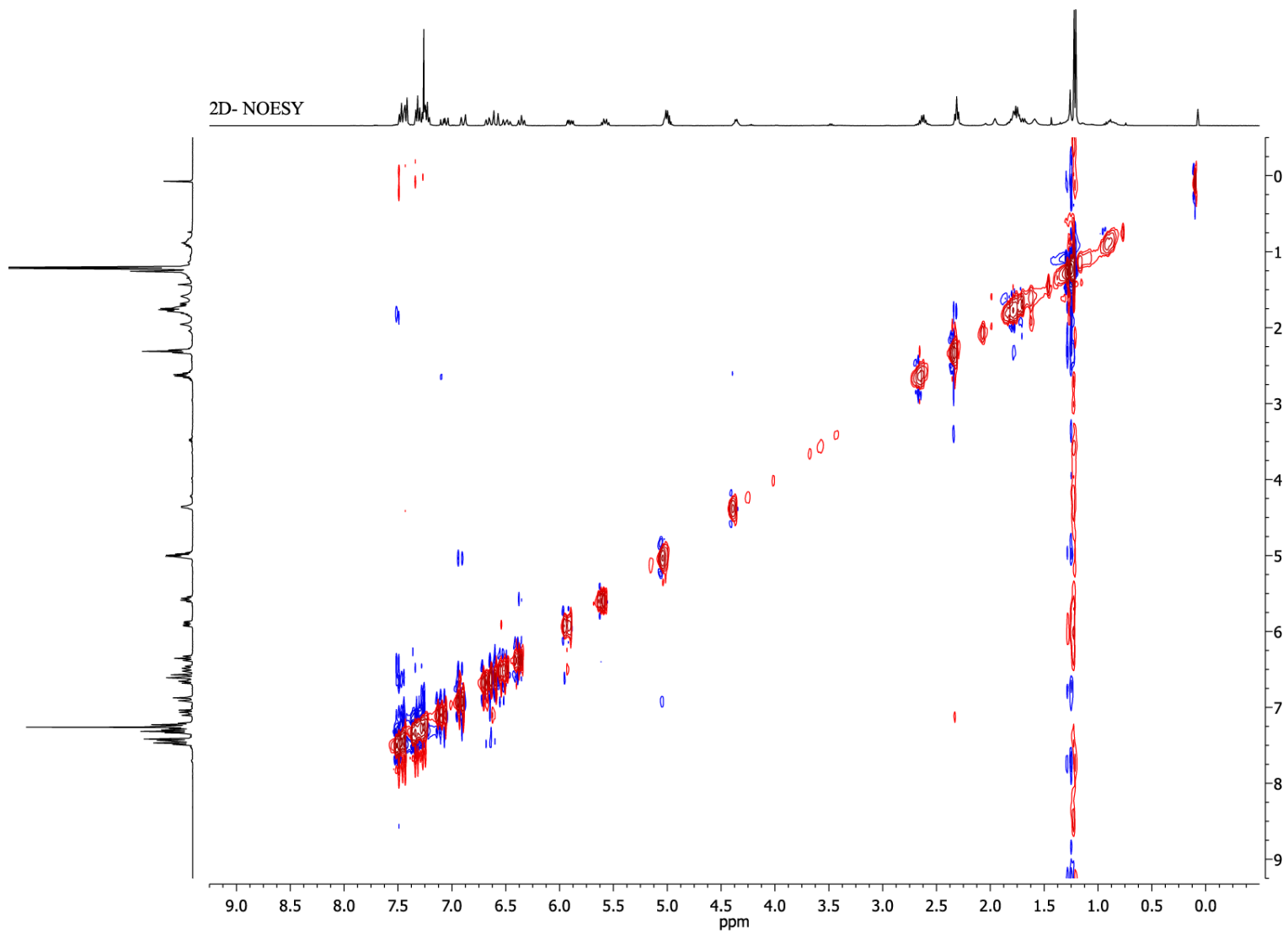


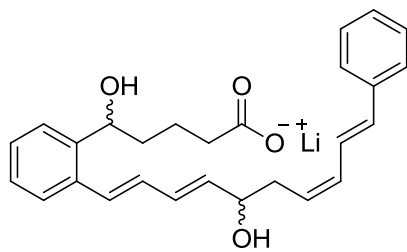




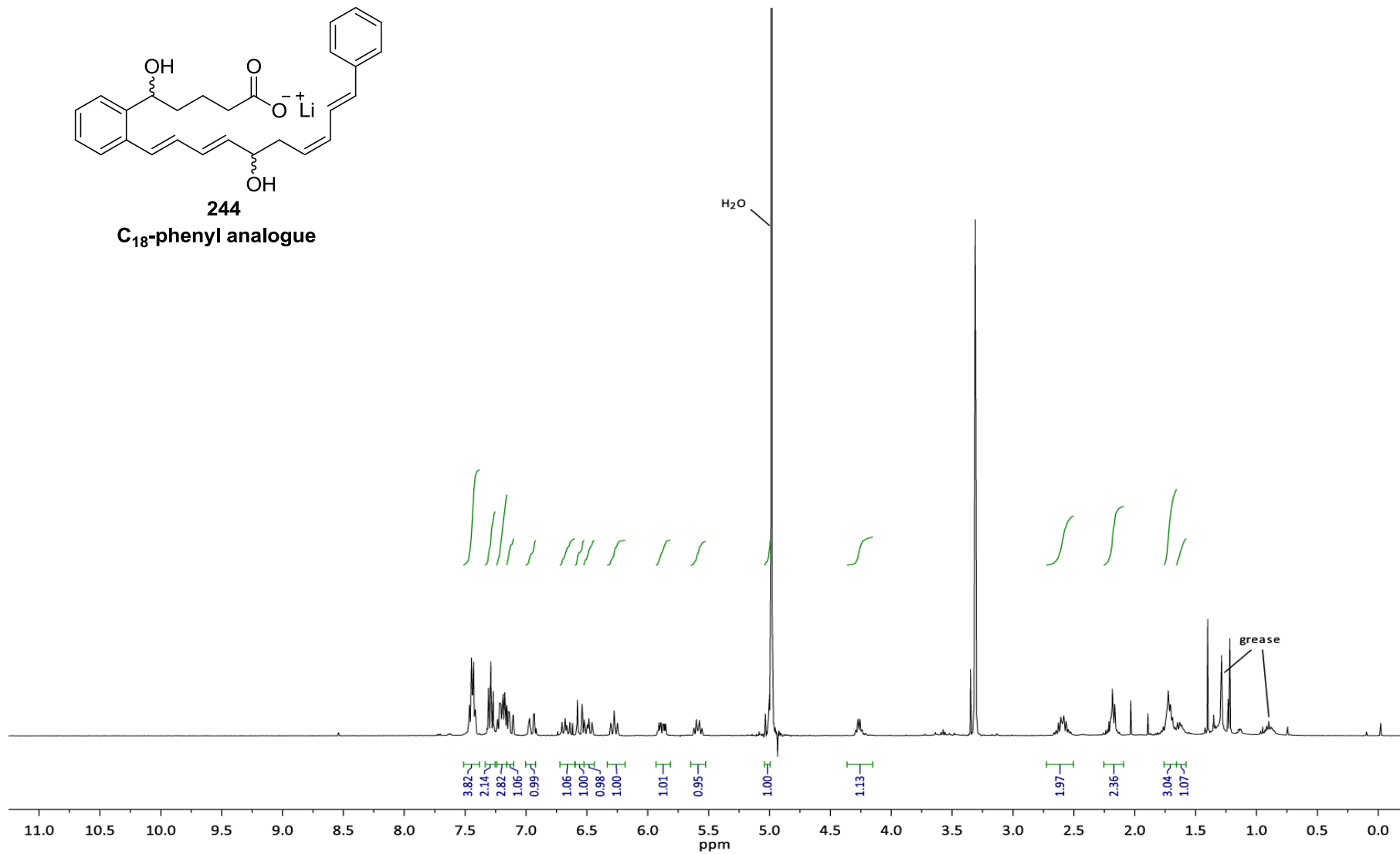


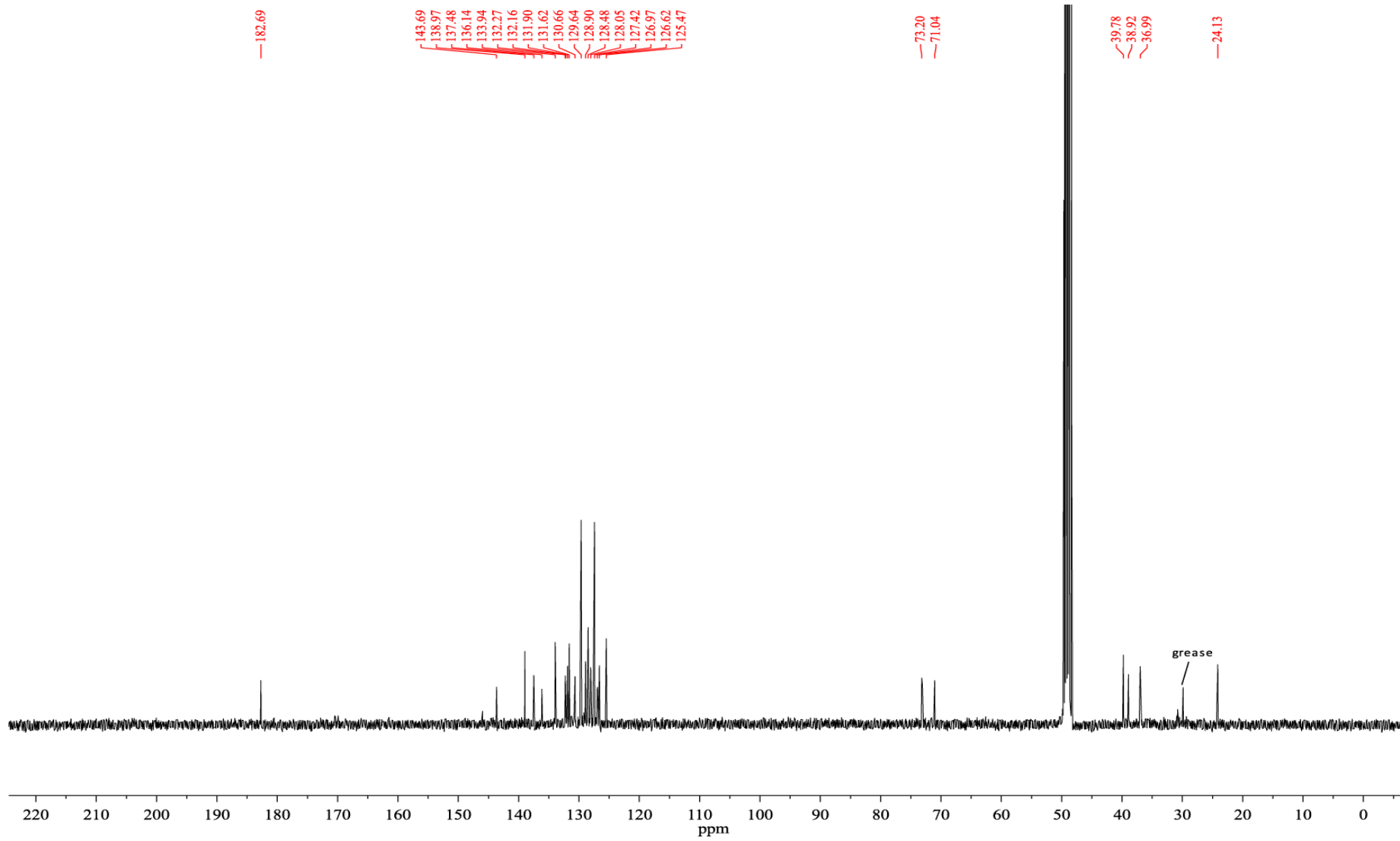
2D- NOESY

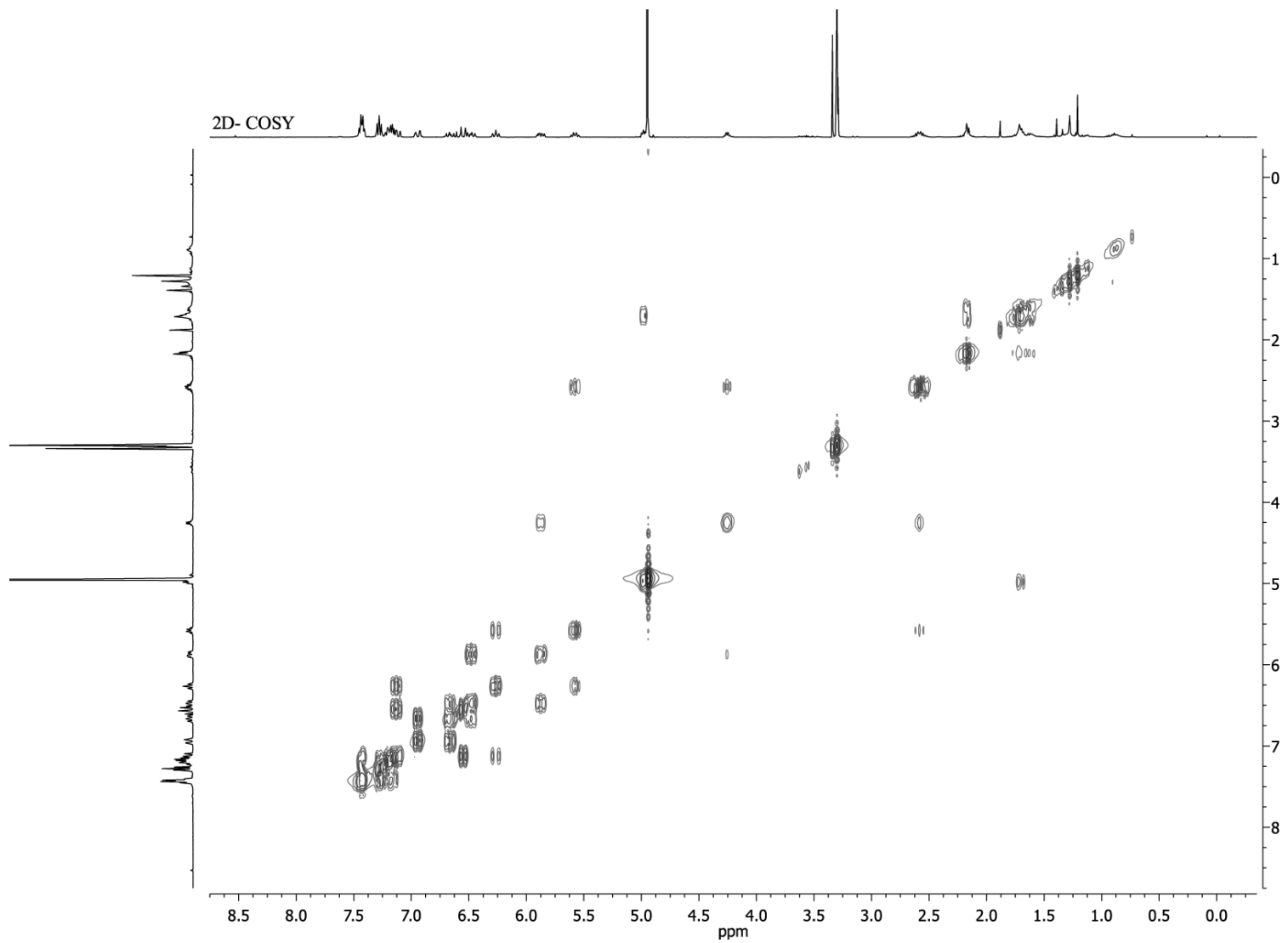


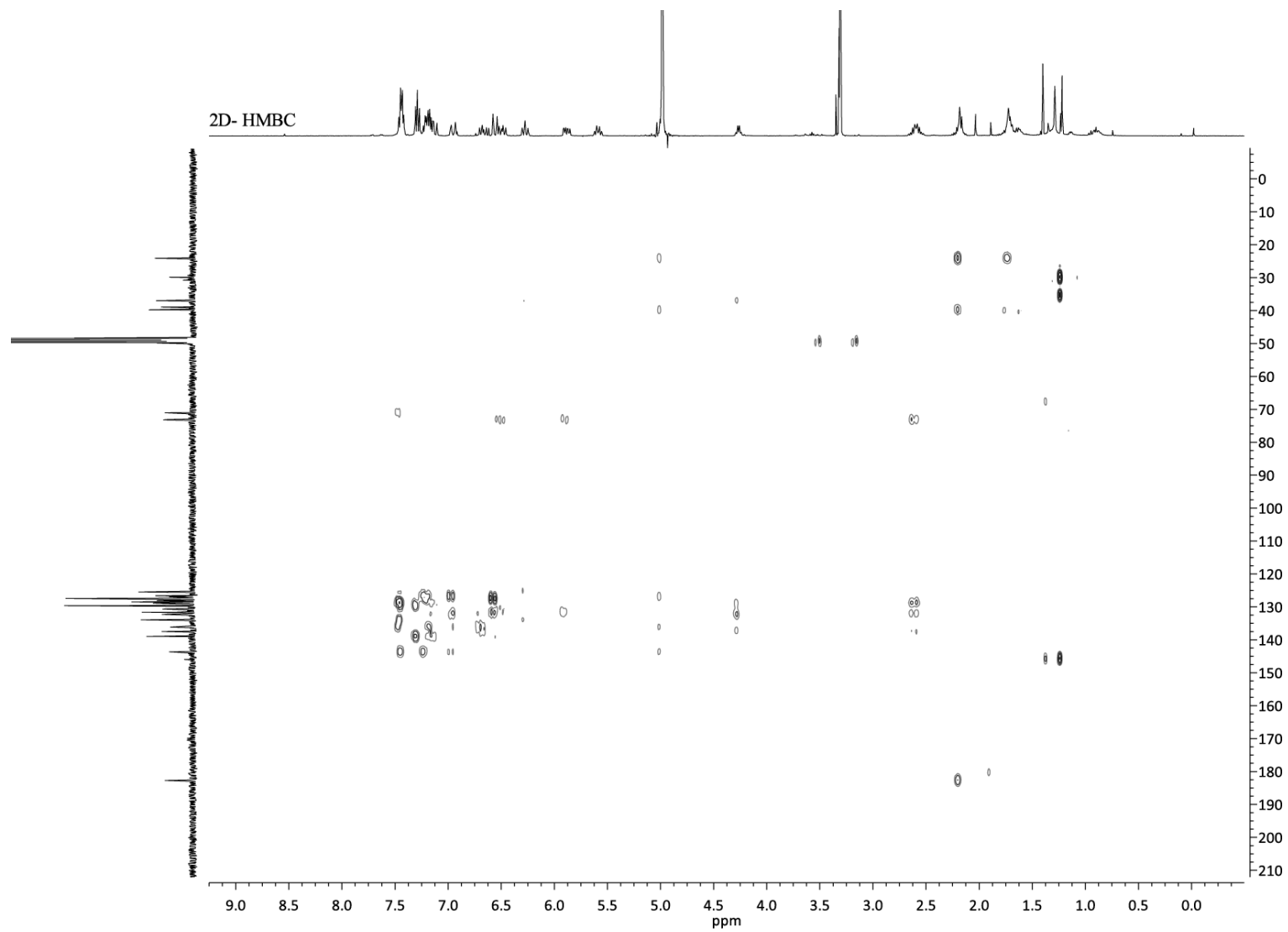


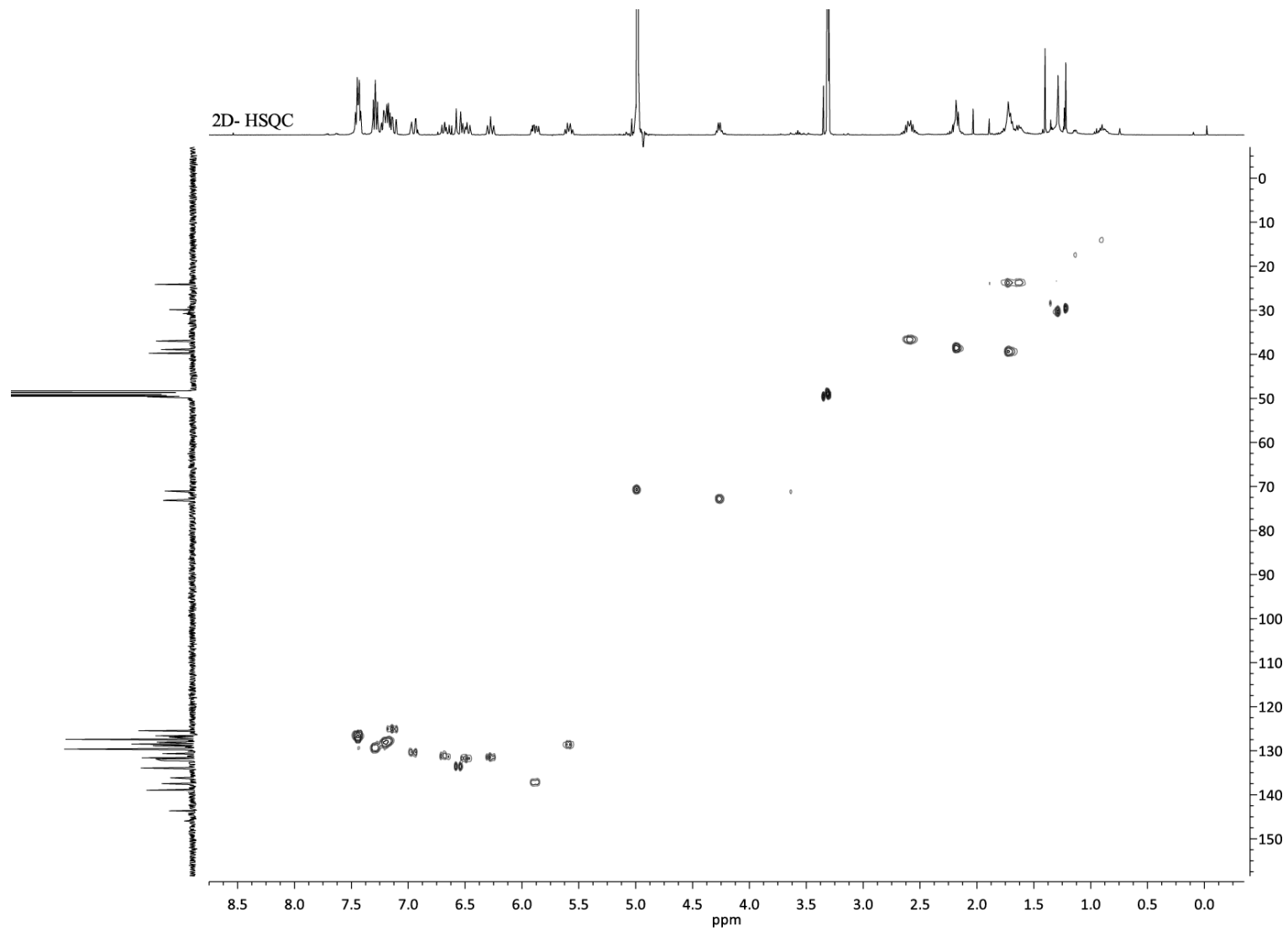
244
C₁₈-phenyl analogue

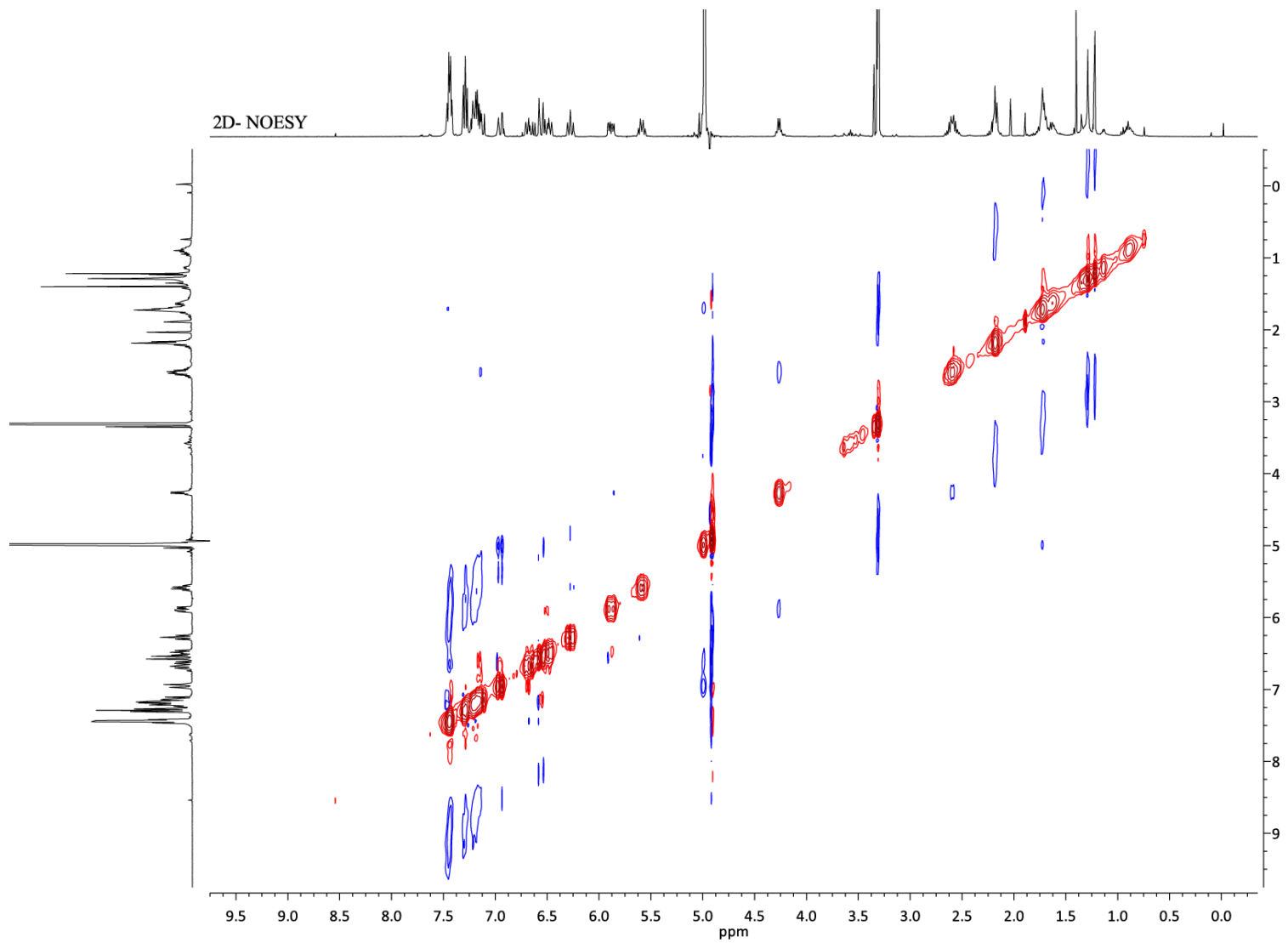




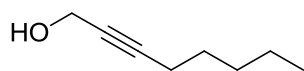




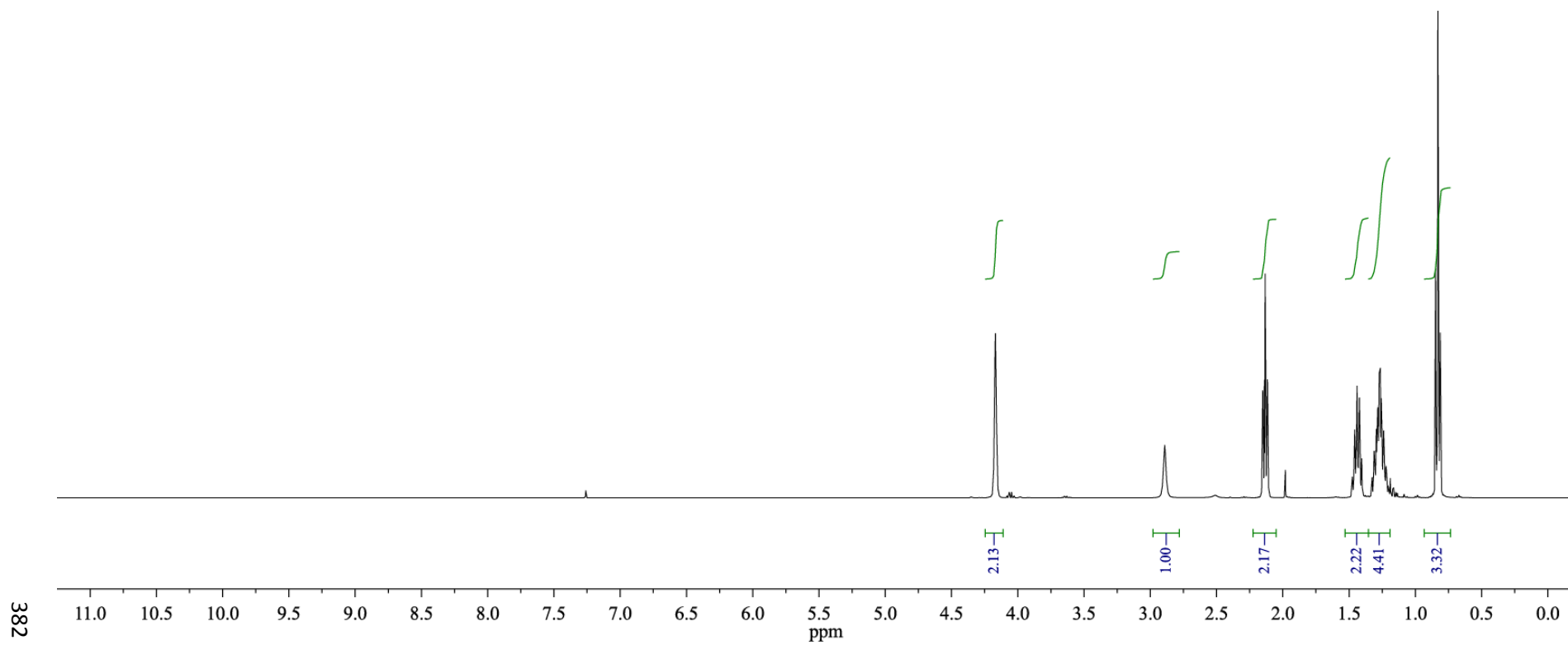


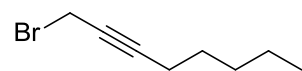


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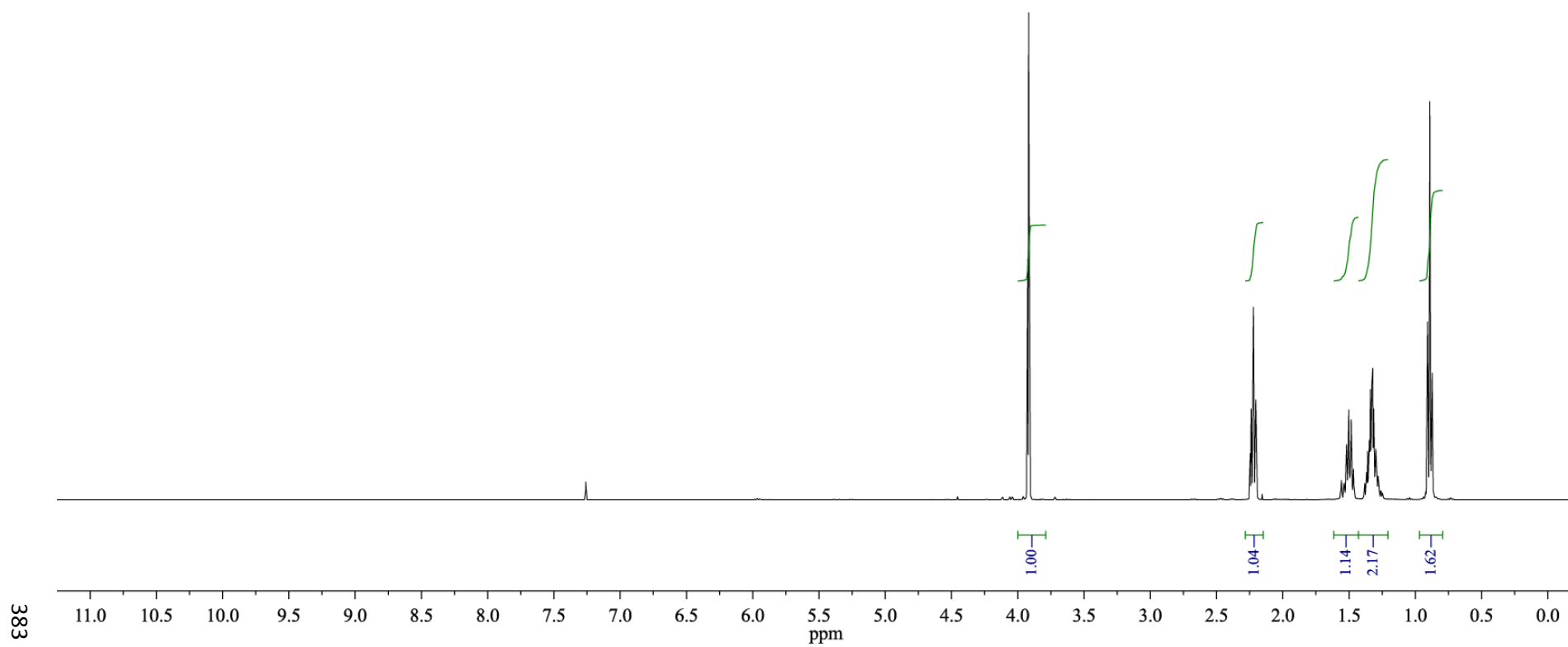


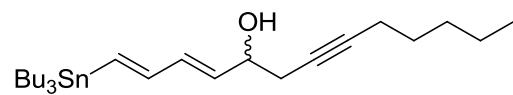
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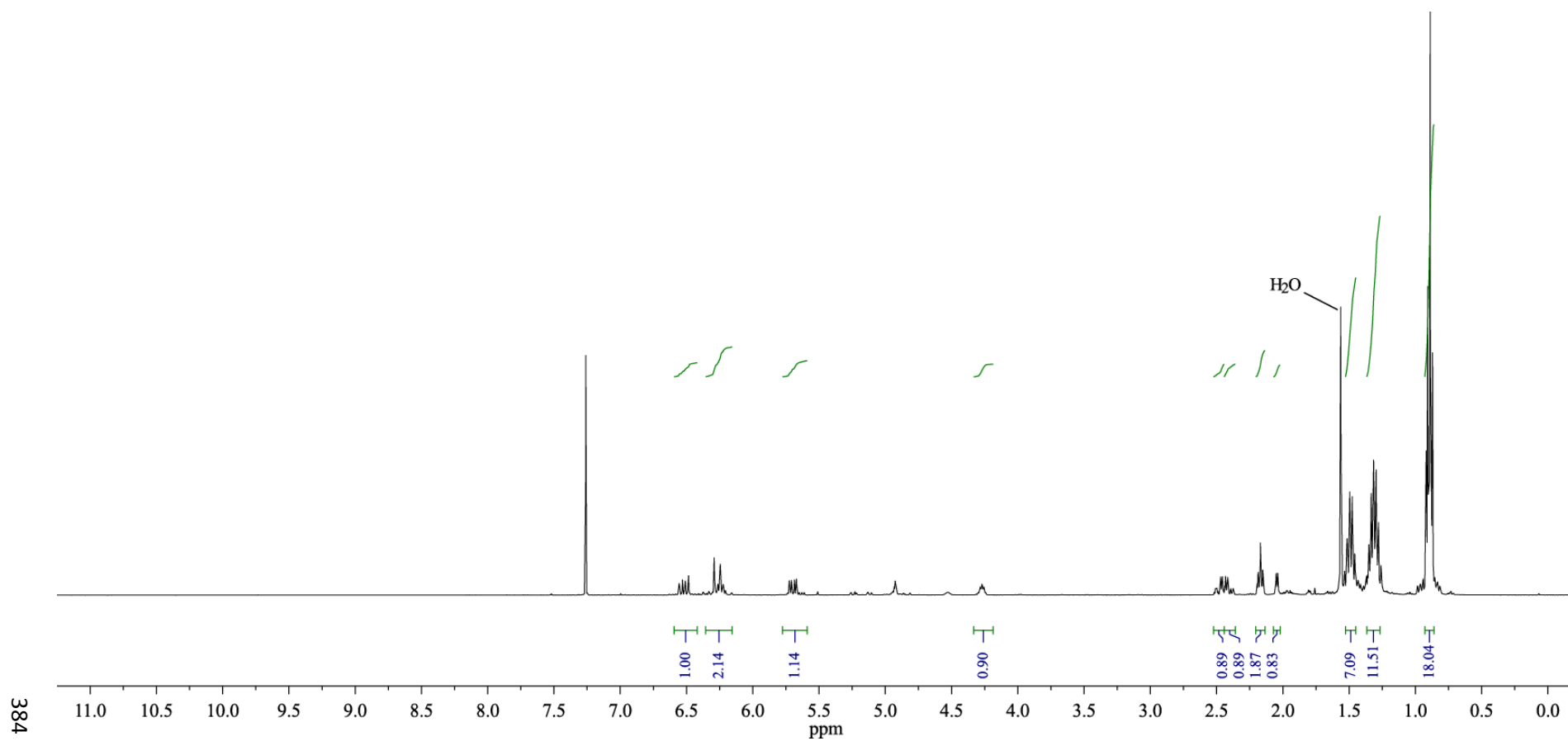


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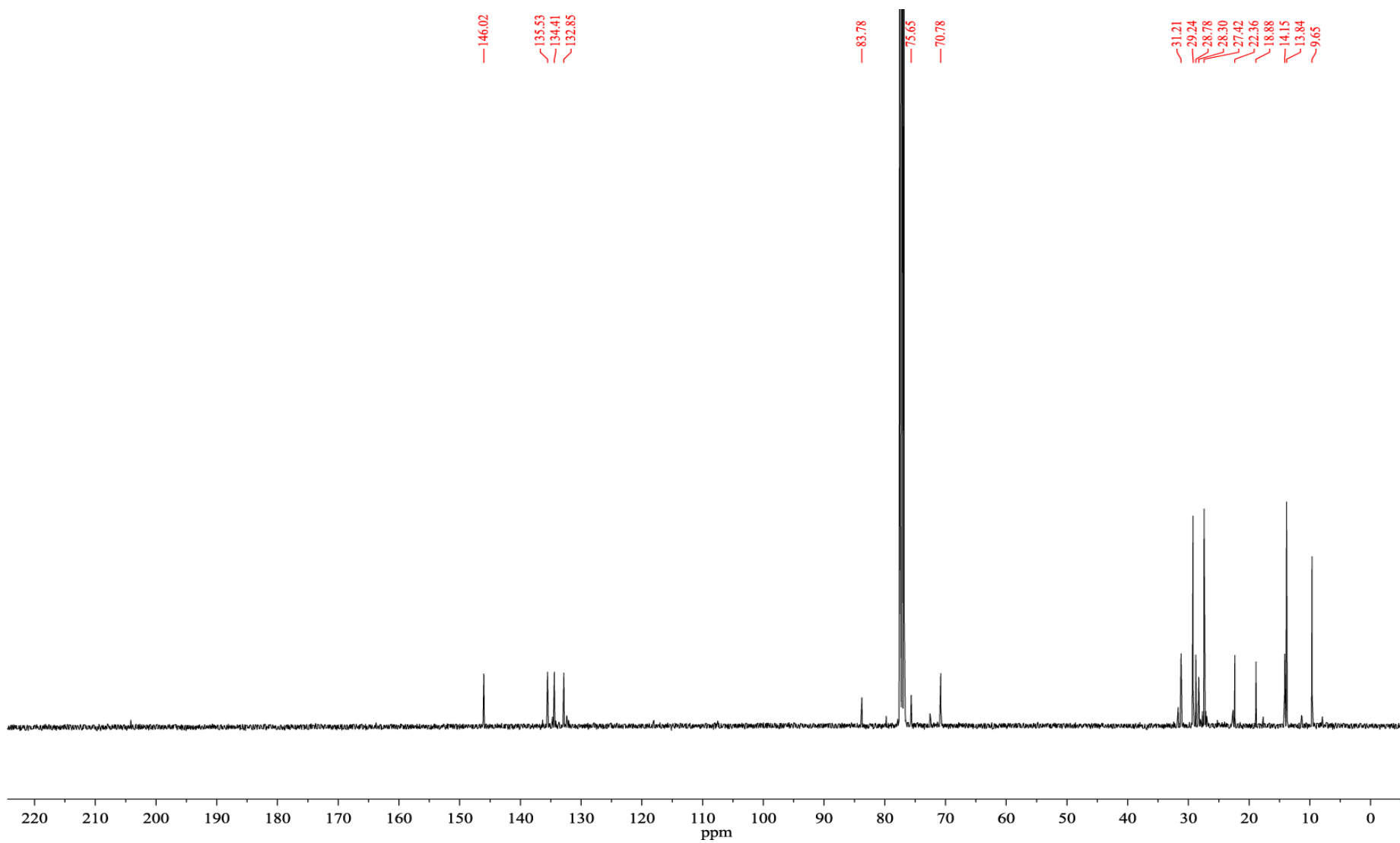


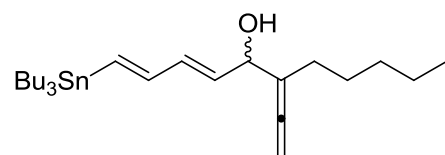


275

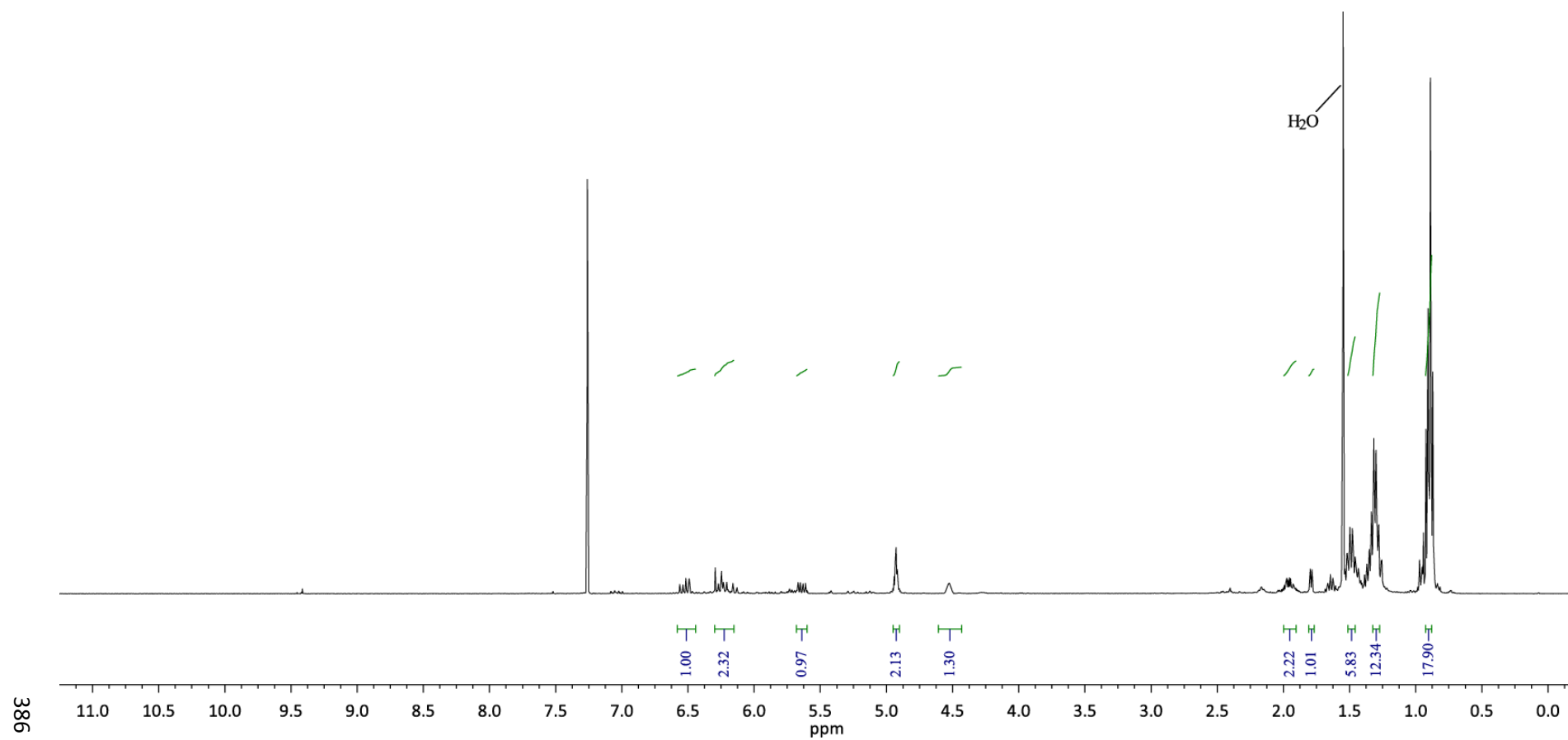


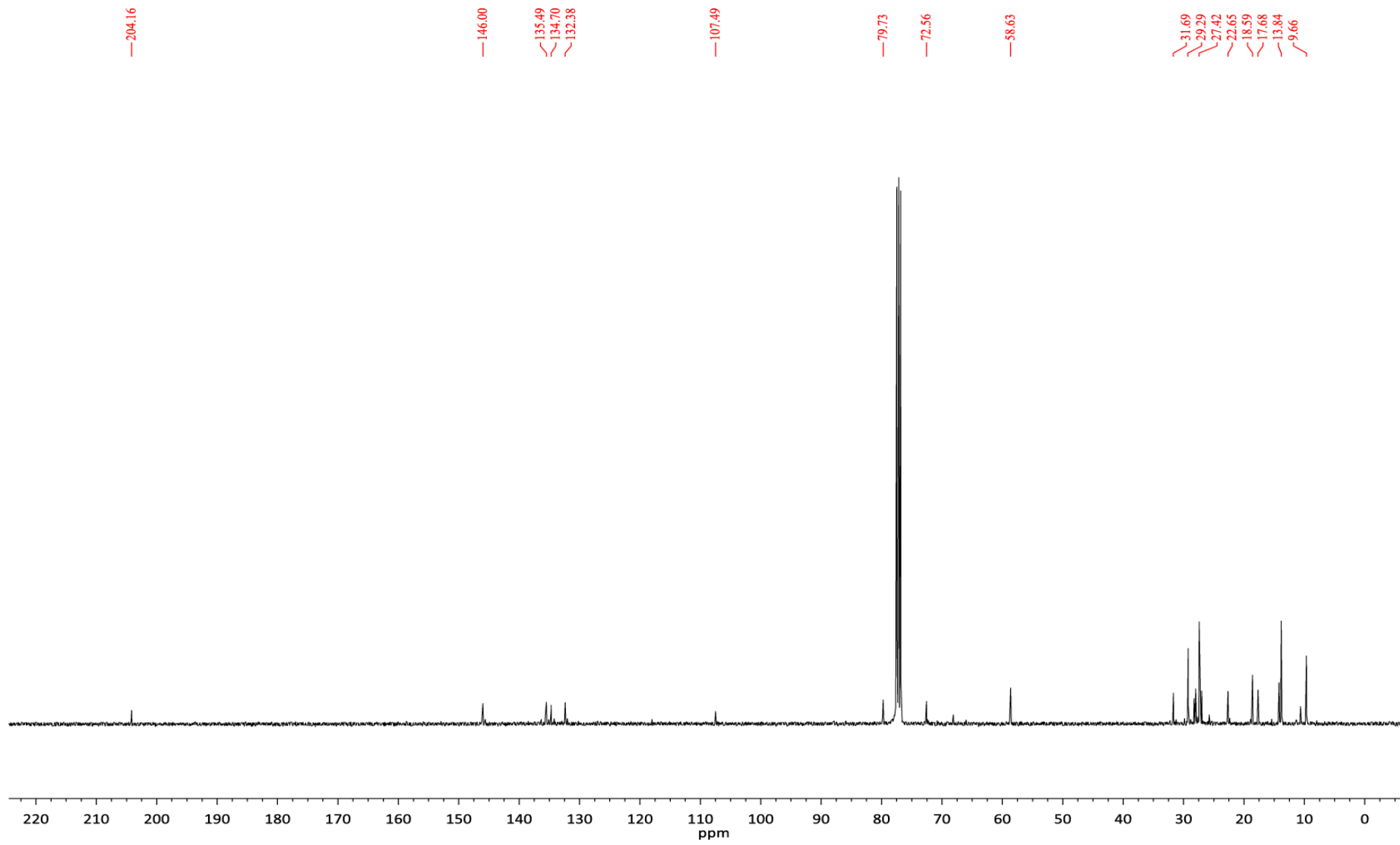
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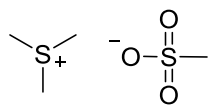




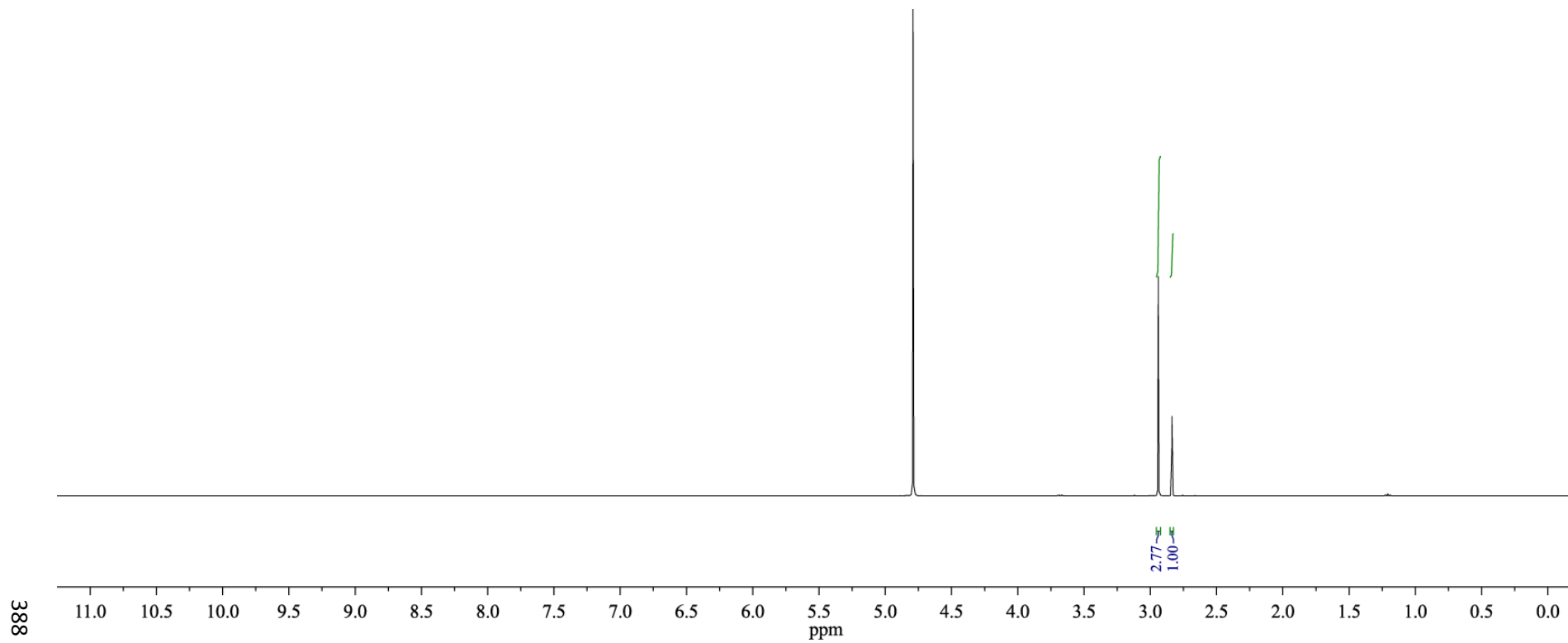
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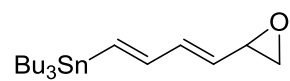




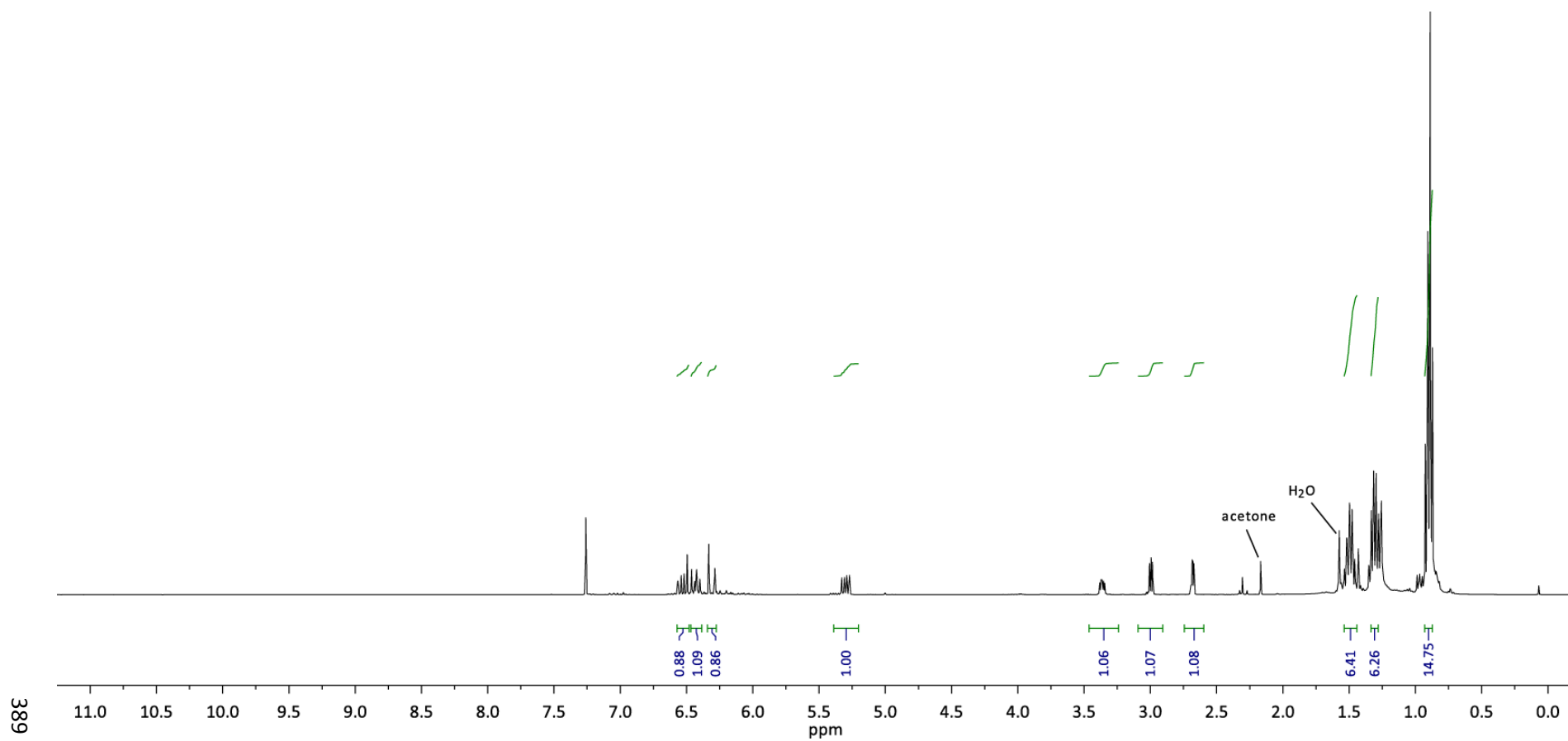


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